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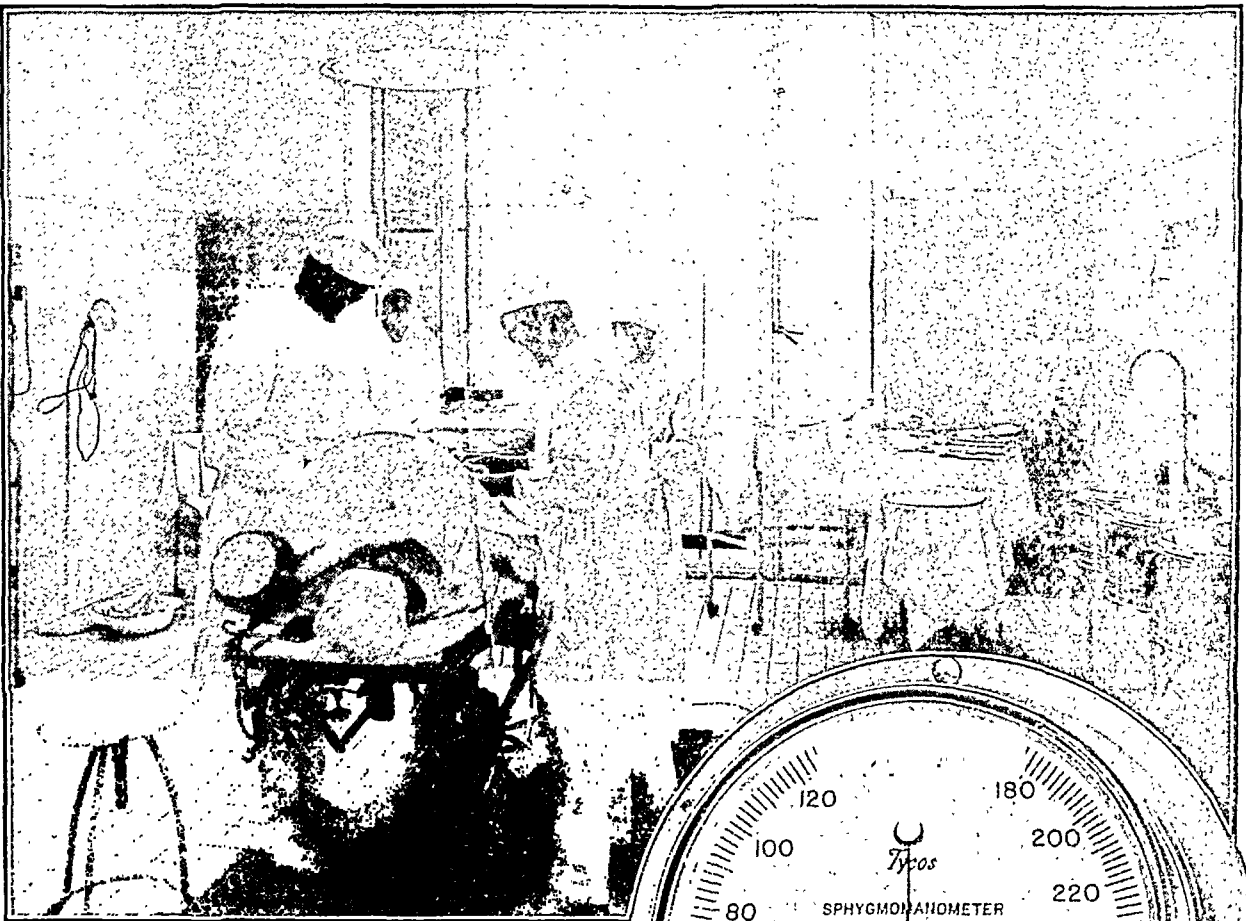
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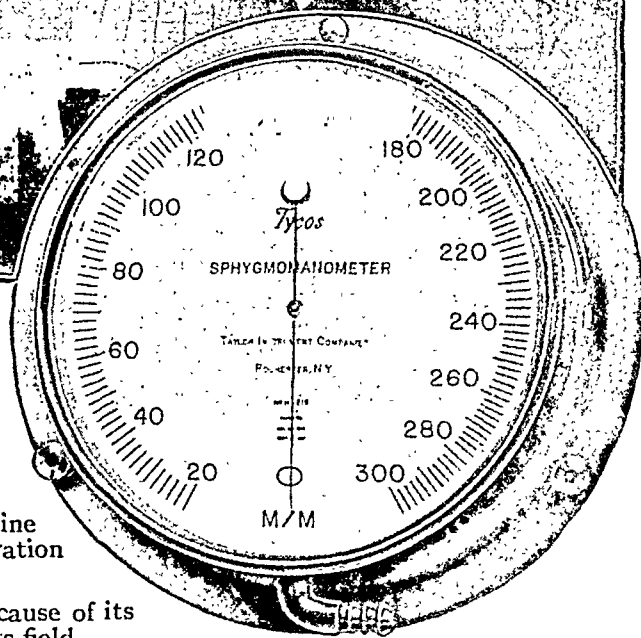
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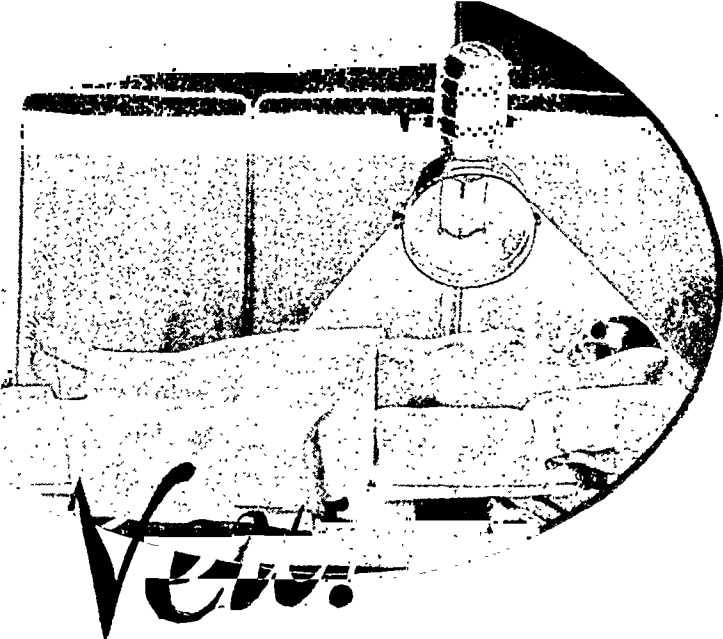
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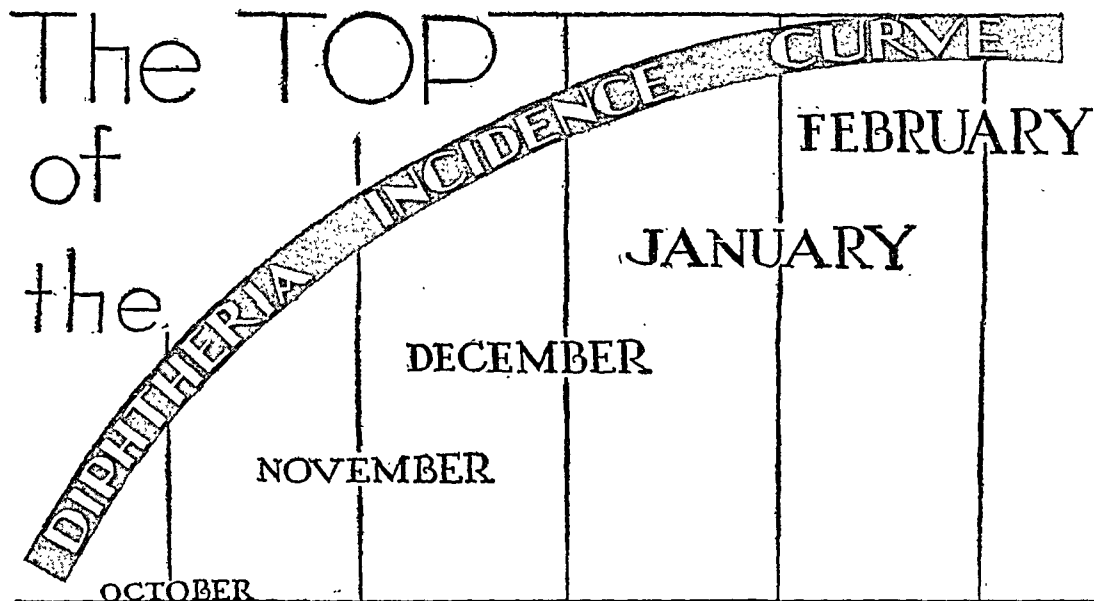
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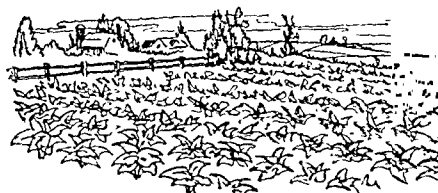
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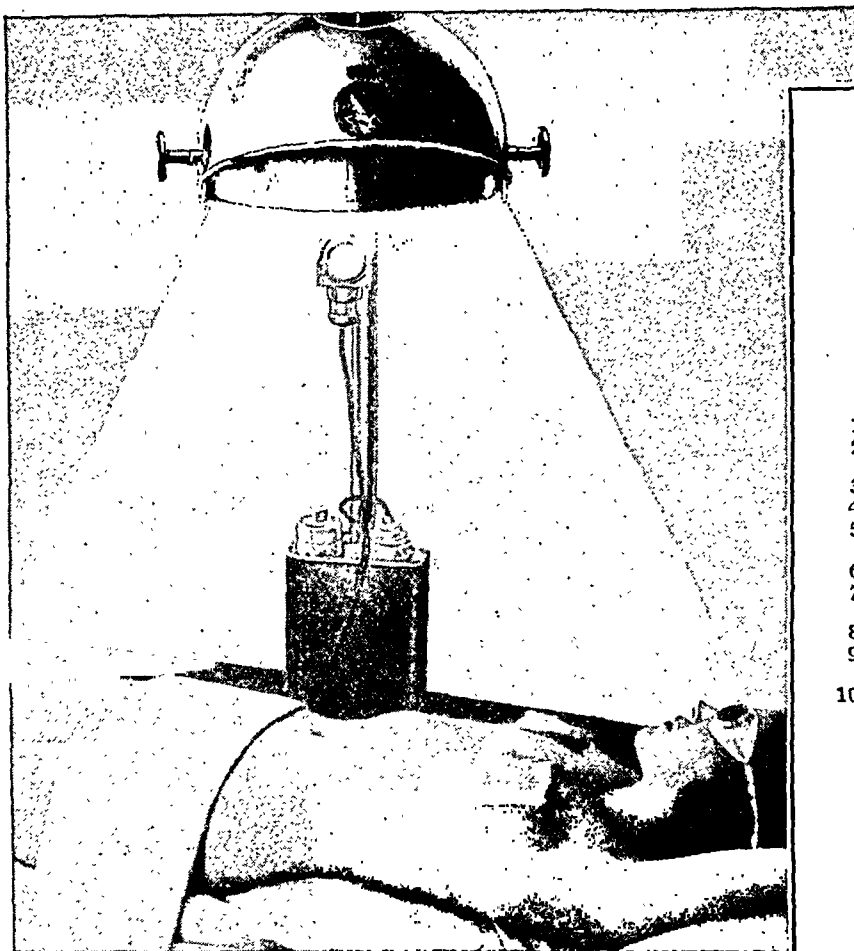
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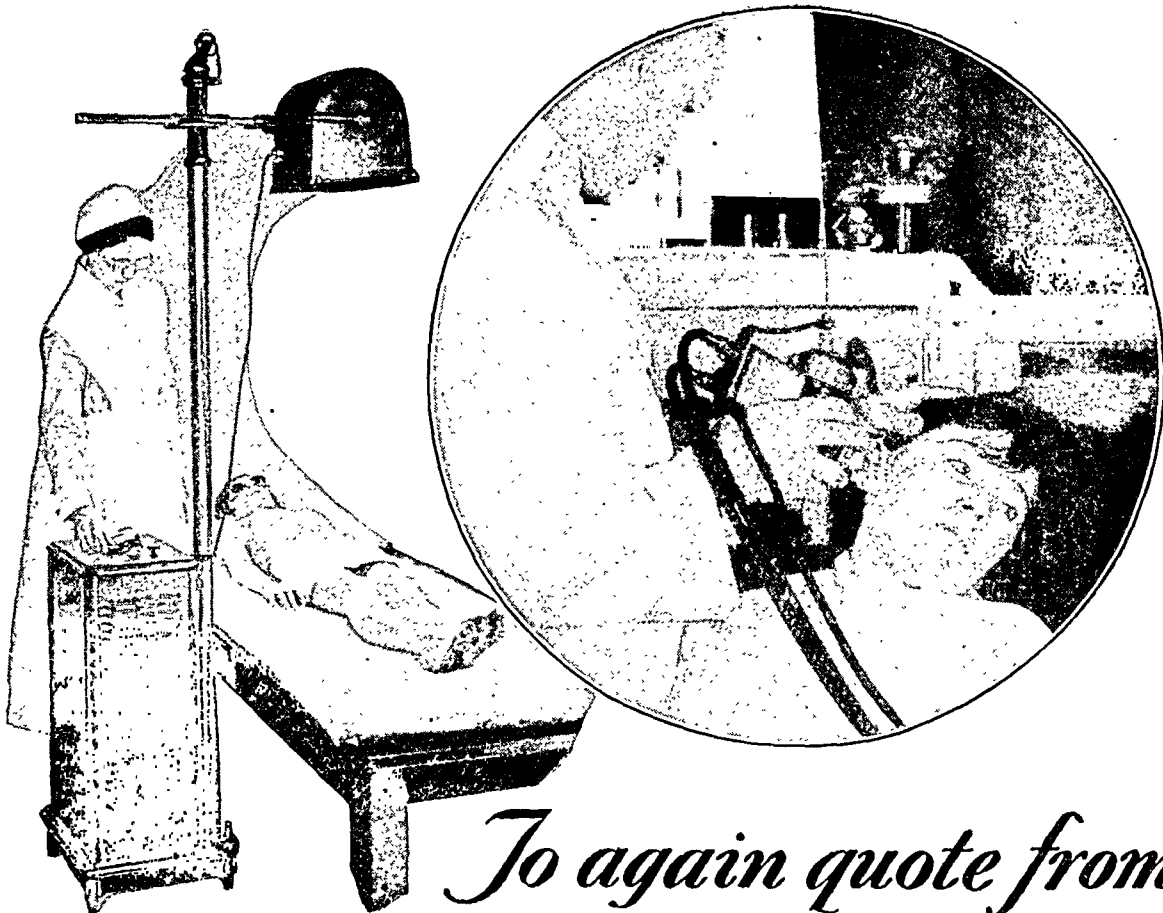
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ORIGINAL ARTICLES.

PEPTIC ULCER OF THE ESOPHAGUS.*

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AND

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PEPTIC ulcer of the esophagus, which closely resembles a similar affection in the stomach and duodenum, occurs most frequently in the lower third of the esophagus. Though this condition is rare, it occurs sufficiently often to be of clinical interest; however, but little attention has been directed to it, especially in this country.

Tilleston¹ classifies all other forms of ulcerations of the esophagus into the following groups, which he considers must be excluded before the diagnosis of peptic ulcer is made: (1) carcinomatous; (2) due to the action of corrosive substances; (3) due to foreign bodies; (4) occurring in the course of acute infectious diseases; (5) decubitus; (6) due to aneurysm; (7) catarrhal; (8) due to traction diverticula; (9) tuberculous; (10) syphilitic; (11) varicose; (12) due to thrush.

These forms of ulceration need not be considered here. The recognition of peptic ulcer of the esophagus has been a matter of comparatively recent date, though isolated cases have been reported as far back as 1839. Von Hacker and Lotheissen,² however, note that many of these were so indefinitely described that the diagnosis of peptic ulcer remains doubtful.

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The first case to be described in literature was that reported by Albers³ in 1839. This was followed by Valleix,⁴ 1844; Reeves,⁵ 1853; Flower,⁶ 1853; Vigla,⁷ 1855; Part,⁸ 1857; Trier,⁹ 1864; Eras,¹⁰ 1866; Knott,¹¹ 1878. In all of these cases, attention was called to the similarity of the lesion to that observed in perforating gastric ulcer. However, Zenker¹² was convinced that the ulceration in these cases was due to carcinoma or perforated traction diverticula or to foreign bodies, or that other causes existed other than actual peptic ulcer.

The 3 first cases which were histologically proven were described by Quincke,¹³ in 1879, and this author deserves the credit of having placed this affection upon a definite pathologic and clinical basis.

Since this period, von Hacker and Lotheissen² have collected 91 cases in all. Of these, however, but a small number have been definitely proven by autopsy or by histologic studies. In some of these cases, scars were noted which on further investigation were observed to be due to peptic ulcer. A few instances of peptic ulcer of the esophagus have been described in children. Spiegelberg¹⁴ and Meier¹⁵ observed fatal hemorrhages in 2 infants, aged five and six years, and Dorn¹⁶ reports a similar outcome in a female, aged five months, due to an ulcer situated just above the cardia. Zuppinger¹⁷ has reported a perforation due to peptic ulcer in a child aged eight years which was fatal. Meulengracht¹⁸ described a peptic ulcer of the esophagus in a female, aged two and three-quarters years, which was associated with dilatation.

Pathology. Peptic ulcers of the esophagus are usually observed in the lower third of the esophagus, though occasionally they are located higher. When occurring high they are usually produced by extension from below though they may be due to unusual causes, such as trauma, traction diverticula or to tuberculosis.

When situated low near the cardia they rarely extend down into the stomach. In six instances collected by Tilleston¹ all of which came to autopsy, the adjacent wall of the stomach was likewise invaded; however, in these cases the cardia was found to be the primary seat of involvement, the ulcer extending directly up into the esophagus. This observation has been confirmed by Eversmann,¹⁹ Fraenkel²⁰ and others:

The size of ulcers of the esophagus varies greatly. They are often small and may again be 8 to 10 cm. in length as has been described by Quincke¹³ and Zahn.²¹ They are usually single, occasionally multiple. The small ulcers are ordinarily round or oval, while the larger ones are irregular in appearance. The large cylindrical ulcers are due in some instances to a confluence of smaller ones (Reher²²).

The right posterolateral wall of the esophagus is usually most frequently involved in this disease. In the instances collected by Tilleston,¹ the ulcer was found in the anterior wall twice, in the posterior wall three times, on the left side twice on the right three times.

Peptic ulcer of the esophagus may be very superficial, appearing only as hemorrhagic erosions or simple mucosal ulcers. On the other hand, they may be extremely deep; and, as in ulcer of the stomach, bloodvessels may become eroded leading to hemorrhage, or perforation may take place or adhesions to neighboring organs may form.

In the superficial ulcers the edges are clean cut, presenting a reddened granular base. In those of long duration, a punched-out appearance is noted with a funnel-shaped base, the base often being smooth with undermined edges. The surrounding membrane is usually normal in appearance. These ulcers, therefore, resemble in many respects ulcer of the stomach and duodenum. It is interesting to note that when perforations do occur they are apt to take place into the abdominal or lesser peritoneal cavity. Perforations of this type have been described by Winkler,²³ Huwald,²⁴ Sencert.²⁵ Perforations may, however, take place instead into the periesophageal connective tissue, pericardium or right or left pleura and gangrene of the lung with pyopneumothorax may result or the aorta may become involved.

As in ulcer of the stomach, healing usually occurs with the production of cicatrices. In the small ulcers, but slight scars occur producing but a minimal degree of puckering. In large ones, contraction takes place with the formation of stenosis. This is usually circumscribed and can be easily recognized by means of fluoroscopy or esophagoscopy. It can be readily dilated but hemorrhage is easily produced; a condition described by Guisez²⁶ as characteristic of peptic ulcer of the esophagus.

According to Tilleston,¹ scars occur in 25 per cent of the cases. Sencert²⁵ considers, however, that healing is far more common than is realized, inasmuch as only severe types of the disease have thus far been recognized. This is probably true, inasmuch as in addition to the presence of the ulcer of the esophagus an identical condition often occurs simultaneously in the stomach and duodenum and the esophageal lesion is thus apt to be overlooked. Microscopically, the usual characteristic inflammatory infiltration without evidence of tuberculosis or cancer is noted, together with slight hemorrhages and occasionally thrombosed arteries. Stoerk was the first to observe in a case of Fraenkel's in Nothnagel's Clinic, glands at the edge of the ulcer, which in all respects resembled those of the stomach. This observation was confirmed in a case noted by Tilleston.¹ Schaffer,²⁷ however, claims that glands of this type may exist in the normal esophagus at times. The examination of the stricture area of the wall of the esophagus reveals sclerotic connective tissue, which invades all the layers of the esophagus and which also surrounds the markedly hypertrophied muscle fibers.

According to von Hacker and Lotheissen,² in 17 instances these ulcers were detected accidentally at autopsy, the immediate cause of death being peritoneal cancer, Bright's disease, gall-bladder

perforation and perforating gastric ulcer. Difficulty may arise in determining the exact etiology when only a cicatrix remains. The similarity to an apparently healed superficial carcinomatous ulcer must be considered or to an ulcer produced by a foreign body or even to other less frequent conditions as perforations from without or perforating traction diverticula.

Etiology The etiology of peptic ulcer of the esophagus is in every respect similar to that of the stomach and duodenum, and, therefore, requires no further discussion here. In order, however, that this affection may occur it is necessary that the cardia remain patent, so that the regurgitated acid gastric secretion may continue its corrosive effect upon the localized diseased area in the mucous membrane of the esophagus. Diseases in which vomiting or regurgitation of food occur therefore play an important rôle in its etiology.

Attention has been called by Tilleston,¹ von Hacker and Lotheissen² and others to the occurrence of this affection associated with stenosis of the pylorus and gastric dilatation which may produce a relative insufficiency of the cardia allowing the continued regurgitation of the acid secretion. This occurred in 23 per cent of the cases collected by Tilleston. As a further proof of the truth of this explanation, von Hacker cites an instance of pyloric stenosis associated with peptic ulcer of the esophagus in which healing of the esophageal lesion was brought about by means of gastroenterostomy.

That regurgitation of the acid gastric juice cannot alone produce ulceration of the esophagus is evidenced by the fact that in many instances of the most aggravated types of pyloric stenosis, this lesion is not produced. The relation of the gastric acidity to esophageal ulceration has been noted by Tilleston¹ in seven instances. Hydrochloric acid was present or increased in six and diminished in one instance.

Among other factors of etiologic significance concerned in the production of ulcer to which attention has been directed by various authorities are local diseases of the bloodvessels (varicosities) of the esophagus (Abram,²⁸ Demel²⁹) nervous disturbances in the form of cardiospasm (Meulengracht,¹⁸ Schmidt³⁰); and trauma (Kraus,³¹ Ortmann³²). It is important to note on the other hand, that Guisez²⁶ is convinced that many of the so-called simple ulcers of the esophagus are actually only localized chronic inflammatory processes which finally terminate in stenosis without undergoing definite ulceration and that simple ulceration of the esophagus is rare. The cause of the stricture in these cases is according to this authority an initial spasm. When the spasm becomes sufficiently prolonged and persistent, permanent dilatation with stenosis is produced. This observation has also been confirmed by McKinney.³³ An interesting fact still remains as Fisher³⁴ has pointed out, which further illustrates the similarity existing between duodenal and esophageal ulcerations, namely, the occurrence of ulcerations of the esophagus following external burns.

Ulcerations have been most frequently observed in adults, the condition being most common between the thirtieth and seventieth years.

The ages of our cases ranged as follows.

Years.	Cases.
20 to 30	1
30 to 40	2
40 to 50	4
50 to 60	3
60 to 70	3
Total	13

According to von Hacker and Lotheissen,² in those instances in which the diagnosis has been arrived at by means of esophagoscopy or by the detection of cicatrices of ulcers, the disease is evenly divided between males and females. Perhaps when the ulcers are present in the lower segment of the esophagus the proportion is slightly in favor of males. In our 13 cases there were 6 males and 7 females. In the cases collected by von Hacker and Lotheissen the diagnosis was made in 26 instances on the living subject; in 22 by means of esophagoscopy, once at operation for perforation into the abdomen (Sencert²⁵) and on three occasions this affection was accidentally noted while operating in the abdomen (Dressman,³⁵ von Mikulicz³⁶).

There were 13 cases of peptic ulcer of the esophagus in our series.

Case History.—The following history presents the most important features of a typical case. B. B., male, aged twenty-eight years, had been complaining of indigestion for the past eight or nine years, consisting of a pressure feeling in the chest around the heart, pyrosis and shortness of breath. Recently, there had been difficulty in deglutition associated with pain at times, beneath the ensiform cartilage and the lower sternum radiating to the back between the shoulder blades. The difficulty in deglutition was more marked recently and especially following solid food. Regurgitation of food was frequent and at times no nourishment was retained for several days. Gaseous eructations and heartburn were frequent and the patient was greatly constipated. He had been living on a very restricted diet, mainly of liquids, and had lost 10 pounds in weight.

On examination, the chest organs were found normal. The abdomen was slightly distended but there were no enlargements or masses present. There was a distinct tenderness in the epigastrium beneath the ensiform cartilage and over the lower sternum. The test meal showed a total acidity of 32, free HCl 18.

The Roentgen ray report was as follows: "The heart and lungs are normal. The esophagus shows a persistent defect at its lower end just above the cardia on fluoroscopic examination as well as in the plates. The stomach, duodenum, and colon are normal." The esophagoscopy examination reveals a definite ulcer with indurated edges above the cardia corresponding in all respects to the picture obtained by means of the Roentgen rays. The diagnosis of chronic ulcer of the lower third of the esophagus was made.

The chart on page 9 presents the important findings of our 13 cases of peptic ulcer of the esophagus.

Symptoms. In most instances, the disease runs an entirely latent course and symptoms are not produced or they may be of so mild a type that the condition may not even be suspected. The initial signs are not sufficiently characteristic to arrive at a diagnosis and only following a considerable period of time are the actual symptoms manifested. In fact, the ulcer may remain latent until perforation or hemorrhage takes place.

The prominent symptoms of this disease are pain, dysphagia, vomiting, hemorrhage and perforation.

1. *Pain.* Pain is a very constant symptom; it occurred in 84 per cent of our cases. It usually appears in the epigastrium, at the xiphoid cartilage or beneath the sternum and frequently radiates to the back between the shoulder blades or over the thorax. Occasionally, there is a definite painful area in the back in the region of the ninth dorsal vertebra. The pain may be mild or intense or of a burning character and is usually increased by pressure in the upper epigastrium or over the lower sternum. According to Sheehan,³⁷ pressure over the lower pole of the spleen will produce pain in this disease.

Pain, however, may occur even without swallowing, but is always increased during the act of deglutition, a sign which distinguishes it from gastric ulcer. It is usually intermittent in type with periods of relief between meals. It is ordinarily less severe when swallowing fluids. Inasmuch as the pain is usually intense, the patient becomes fearful of food, restricts his diet and becomes very much undernourished.

2. *Dysphagia.* Difficulty in deglutition is also a very prominent sign of the disease. It occurred in all of our cases. At first it is observed only in taking solids, but later there is even great difficulty with liquids and finally but very small amounts of nourishment can be consumed. The difficulty in swallowing is produced by spasm of the esophagus and in consequence regurgitation of food takes place, nutrition is disturbed and the patient loses flesh and strength.

3. *Vomiting.* Vomiting was observed in 54 per cent of our cases. It is produced at first by spasm, later frequently as the result of actual stricture. Regurgitation of food is far more frequent than actual vomiting with which it is often confused. According to von Hacker and Lotheissen,² if large amounts of food are regurgitated it may be concluded that a stenosis has been produced as the result of the ulcer.

4. *Hemorrhage.* According to Tilleston,¹ hemorrhage occurs in 53 per cent of the cases but was present in but 23 per cent of ours. At times but small amounts of red or reddish-brown blood are regurgitated, occasionally larger quantities of dark blood of the coffee-ground variety are vomited resulting from the accumulation of small amounts which have slowly passed into the stomach. In some instances, the blood passes entirely or partly through the bowel,

and is detected as melena. In most instances, according to our experience, even when visible hemorrhage is not observed, occult blood is found in the stools. In consequence of these hemorrhages, anemia and loss of strength is produced and finally great loss of flesh and even cachexia occur. In the patient reported by Zahn,²¹ death followed as the result of the onset of pernicious anemia. The source of the hemorrhage is from an erosion of a bloodvessel in the ulcer and should bleeding be excessive death may quickly ensue. It is extremely difficult at times to determine whether the hemorrhage arises from the esophagus or stomach. This difficulty is even increased when one recognizes the fact that an ulcer of the stomach or duodenum and esophagus may coëxist. Curshmann³⁸ has pointed out that in hemorrhage from a ruptured esophageal vessel, the blood usually pours out without producing nausea and straining, as one usually observes in gastric hemorrhage.

Perforation. Perforation occurs in 14 per cent of cases according to Tilleston¹ and is usually fatal. Its presence is indicated by the signs of the sudden onset of a perforative peritonitis or by sudden pain in the chest with dyspnea and collapse followed by pneumothorax or hydropneumothorax. This complication did not occur in any of our cases.

Diagnosis. There is usually great difficulty in arriving at a diagnosis of peptic ulcer of the esophagus and not uncommonly the diagnosis is not made until a fatal complication, such as hemorrhage or perforation, occurs. In other instances, the diagnosis remains obscure until the later stages when stricture with dilatation of the esophagus manifests itself. In some cases, it may be made with a considerable degree of certainty. Whenever ulceration occurs in the lower esophagus, the peptic form should be suspected and the diagnosis only becomes certain if other varieties can be excluded. In arriving at the diagnosis the symptom of pain associated with dysphagia situated beneath the sternum and radiating between the shoulder blades is of great importance. In addition, there is frequently vomiting or regurgitation of food; at first immediately but later following dilatation some time after the ingestion of food, and then usually in large amounts. Tenderness over the lower portion of the sternum or upper epigastrium and in the back is usually present. Additional evidence in favor of this affection is obtained from the coëxistent history of ulceration of the stomach or duodenum as well as by the detection of a constant blood-discolored area following the passage of a thread according to the Einhorn method and the presence of occult blood in the stools. The employment of bougies as an aid in the diagnosis of this condition is not to be recommended. These instruments are extremely dangerous when used in this affection and are apt to produce hemorrhage or perforation even though passed over a thread anchored in the bowel.

Since the advent of fluoroscopy and esophagoscopy, a more com-

plete investigation of the esophagus has been made possible. The Roentgen ray examination may render considerable aid in diagnosis and should always be undertaken before esophagoscopy is performed. Special attention to the technique must be followed in order to note small lesions which may otherwise be overlooked. The subject is at first fluoroscoped in the anteroposterior, lateral, and oblique positions in order to bring the esophagus and the suspected lesion into view. The usual liquid meal of barium and water or with acacia is administered and the opaque meal is viewed as it descends through the esophagus. Four types of defects may be observed in the esophagus: (1) mucosal erosions; (2) niche or penetrating; (3) spastic defects; (4) perforating.

In mucosal erosions, defects are not as a rule observed in the Roentgen ray examination, but frequently in this type of ulcer spastic phenomena are noted which are suggestive of ulcer when constantly present. A small fleck of barium may be observed in the ulcer area. A definite diagnosis can be made from the symptoms together with the esophagoscopic findings.

The niche or penetrating type of ulcer is the most frequent Roentgen ray finding. The filling defect is quite as much characteristic of ulcer as one notes in gastric ulcer. These ulcers are usually small, the craters shallow, but may also be deep, filling and emptying readily as the meal passes over the lesion. They are best observed when the patient is allowed to swallow the liquid meal slowly, and a small fleck of barium is noted in the ulcer crater, which is usually seen when the esophagus is empty. Occasionally, this form of ulcer may be of large size, resembling a diverticulum. These ulcers are usually single but in several instances in our series two ulcers have been found in various portions of the esophagus. Moreover, in a number of our cases we have noted that the patient complained of distress or pain when the meal passed over the ulcerated area. This sign is not only typical of a benign ulcer but is also frequently observed in early cases of carcinoma. The niche type of defect is pathognomonic of ulcer of the esophagus.

Spastic defects are frequently observed on the films as well as by fluoroscopic examination. Three types of defects are usually noted: (1) simple transient spastic defects causing retardation to the opaque meal; (2) a tapering defect of the esophagus toward the cardia; (3) an indentation, resembling an incisura simulating the spastic phenomena observed in gastric ulcer occurring opposite the ulcer defect. This may be noted especially when the ulcer occurs in the lower third and when there is a patency of the cardioesophageal opening; the spastic defect being constant, and the esophagus usually slightly dilated in this area. Cardioesophageal patency occurred in 10 of our cases examined; the type varied from a slight spasm to a marked constriction.

The perforating type of ulcer occurs as a complication of this

IMPORTANT FINDINGS OF 13 CASES OF PEPTIC ULCER OF THE ESOPHAGUS.

Name.	Sex.	Age.	Duration.	Site.	Dysphagia.	Substernal discomfort.	Pain.	Pyrosis.	Vomiting and regurgitation.	Hemorrhage.	Roentgen ray findings.	Esophagosopic examination.
1. B. B.	Male	28	8 yrs.	Lower third	+	+	+	+	+	0	Patency of cardioesophageal opening; small defect	Small eroded ulcer above the cardia, with indurated edges.
2. H. G.	Female	47	4 mos.	Middle third	+	+	+	0	0	0	Small filling defect	Ulcer on right wall, not indurated.
3. D. E.	Female	50	3 mos.	Upper third	+	+	+	+	+	0	Obstruction, marked spasm, and irregular defect in upper third, spasm in lower third	Indurated ulcer with narrowing of lumen of esophagus.
4. J. J. M.	Male	65	1 yr.	Lower third	+	+	+	0	0	0	Large circumscribed dilatation 4 cm. in diameter, lower end, patency of opening	Large indurated ulcer with dilatation.
5. W. F. W.	Male	47	1 yr.	Lower third	+	+	+	+	+	+	Patency of cardioesophageal opening, with small defect	Ulcer of moderate size with smooth edges and indurated base.
6. S. S.	Male	35	2 yrs.	Lower third	+	+	+	0	+	0	Patency, slight dilatation with small defect	Well-defined ulcerated area with indurated edges
7. W. T. S.	Female	68	Many yrs.	Lower third	+	+	+	+	+	0	Patency of cardioesophageal opening, lumen irregular, small defect, slight dilatation	Ulceration medium sized with dilatation above.
8. H. T.	Female	43	2 yrs.	Lower third	+	+	+	+	+	0	Penetrating ulcer 1 cm. in diameter	Not made.
9. R. C.	Female	55	1 yr.	Lower third	+	+	+	0	0	+	Small filling defect	Indurated ulcer, mucous membrane extremely red and thickened, large bleeding.
10. T. S.	Female	56	4 yrs.	Lower third	+	+	0	0	0	0	Patency of cardioesophageal opening, dilated lumen, irregular, shows a constriction	Large indurated ulcer, thickened mucous membrane.
11. M. B.	Male	42	1 yr.	Upper third	+	+	+	0	0	0	Small defect 5 mm. in diameter, middle third	Small ulcer, edges smooth and not indurated.
12. A. C. C.	Male	31	10 dys.	Upper third	+	+	0	0	0	0	Small defect 3 mm. in diameter	Ulcer $\frac{1}{2}$ cm. in diameter, edges and base indurated, mucous membrane very red.
13. M. L.	Female	60	Many yrs.	Upper and lower third	+	+	+	+	+	+	Two penetrating ulcer defects, one in upper and one in lower third	Not made.

affection, but is rarely observed by the Roentgen ray inasmuch as the patient is ordinarily so extremely ill, that this method of examination cannot be undertaken. This type of ulcer will be fully described in a later experimental communication.

The fluoroscopic examination is the method of choice to be undertaken in the study of the esophagus, as the subject may be placed in the various positions for a study of the esophageal outline. Films, however, are always taken in at least two positions to confirm the fluoroscopic findings. It is also occasionally necessary to have the patient in the recumbent posture drink the opaque meal through a straw in order to observe the esophagus properly filled, but as a rule in ulcer it is usually best to take the films both when filled and empty, as a small amount of barium will frequently remain in the ulcer crater sufficiently long to be demonstrated on the films.

Stricture, as a complication of this condition, occasionally occurs and gives similar Roentgen signs as strictures due to other causes, such as lye or acid burns. In this condition, the esophagus shows obstructive signs with marked dilatation, which must be differentiated from cardiospasm. Marked dilatation was noted in one instance, while small localized circumscribed dilatations were observed in 3 instances. Obstruction was noted in 1 case and slight retardation of the opaque meal observed in 6 instances. Inflammatory masses with induration were observed in 2 instances.

Defects were observed in all of our cases of ulcer of the esophagus, the lower third being the most frequent site. In 2 instances two ulcers were noted, one in the upper and one in the lower end, and in 1 of the cases a gastric ulcer was also observed. In another instance duodenal ulcer was associated with the esophageal ulcer.

The use of the esophagoscope has been of the greatest service in the diagnosis of peptic ulcer of the esophagus and considerable advance in the clinical study of the disease has been accomplished by means of this instrument. Its employment, however, is not a harmless procedure and must be practised with great caution.

Inasmuch as the tube should be introduced while its passage is being visualized, it may be applied under skillful hands with a minimal degree of risk. The ulcer may be observed without the tube actually reaching it and direct information may be observed concerning its presence which cannot be obtained by any other method. In doubtful cases biopsy of the wall will definitely clear up the diagnosis, though this procedure is extremely dangerous. Ulcerations may be mistaken for cancer as occurred in the cases reported by Starck³⁹ and Tapia⁴⁰ in which this error was made while the further course of this affection finally cleared up the diagnosis.

During the past few years, the diagnosis of peptic ulcer of the esophagus has been definitely determined by means of this instrument in many instances. Von Hacker and Lotheissen,² in 1920, collected 22 cases in 14 of which the ulcerations were directly

visualized and in 8 the scars of the ulcers, but there are now undoubtedly many more which have not been recorded. Under direct visualization the ulcer lies usually lengthwise and presents a definite loss of substance. The ulcers are usually small, covered with a grayish exudate which bleeds readily; occasionally, especially when the ulcer is situated at the cardioesophageal opening, the ulceration may be very large. The edges are somewhat thickened, sharply defined, showing a definite crater, the base of which is filled with granulation tissue. The surrounding area is frequently indurated and thickened as a result of the chronic inflammatory lesion. At times a bleeding ulcer will be observed, but this finding is more frequently found in the early and acute type. The ulcer bleeds readily when touched by the applicator, which also produces extreme pain in this region. The lumen is not as a rule narrowed, excepting in old chronic untreated cases of long standing in which stenosis with stricture may be found. Spasm of the esophagus is not usually observed in the esophagosopic examination. Strictures of the esophagus secondary to simple peptic ulcerations are, however, rare but are commonly found in cases resulting from burns due to lye or concentrated acids. These ulcers may, however, resemble chronic peptic ulcers, excepting that they produce large scars and usually cause strictures. Uncomplicated peptic ulcers heal readily under proper treatment and usually show no extensive scar formation. When stricture is observed, the esophagus becomes more markedly dilated, on account of a long-standing obstruction.

Induration and thickening of the esophageal wall may be observed in benign as well as in malignant conditions, and at times it is extremely difficult to determine the exact nature of the lesion.

Fixation of the esophageal wall is an infrequent finding in chronic ulcerations but occurs most frequently in malignant ulceration. This condition occurred in 2 instances in our series, in 1 confirmed by biopsy.

Differential Diagnosis. Peptic ulcers of the esophagus must be differentiated from similar ulcerations occurring in the stomach and duodenum as well as from ulcers in the esophagus due to other causes.

This form of ulceration is distinguished from ulcer of the stomach and duodenum in that the pain appears immediately upon swallowing food and is associated with difficulty in deglutition, while in gastric and duodenal ulcer this symptom appears late, and is not associated with dysphagia. The hemorrhages accompanying ulcer of the esophagus occur suddenly and are violent, occurring without nausea or straining, while in ulcer of the stomach and duodenum there is usually considerable nausea and straining. Tenderness over the sternum is characteristic of esophageal ulceration, epigastric tenderness is more common in the gastric and duodenal disease.

In the differential diagnosis between peptic ulcer of the esophagus from ulcerations due to other causes, there is ordinarily but slight

difficulty. The history of the occurrence of trauma or the history of a preceding infectious disease is usually sufficient to quickly distinguish these affections.

Rupture of varicose veins of the esophagus with consequent hemorrhage may at times cause confusion. Pain and dysphagia are, however, absent in these cases and the usual associated signs of cirrhosis of the liver will ordinarily clear up the diagnosis.

Luetic ulceration can usually be ruled out by means of the Wassermann test, and the tuberculous and the carcinomatous forms by means of the Roentgen ray and esophagoscopy with the addition, if necessary, of biopsy. When stenosis occurs followed by a greater or less degree of dilatation of the esophagus without the previous characteristic history of peptic ulceration, it may become difficult to distinguish this form of stenosis from other varieties. Stenosis following ulcerations due to corrosive poisons or due to foreign bodies can usually be determined by the history; diffuse dilatation due to cardiospasm by means of the Roentgen ray and esophagoscopy. Carcinomatous stricture is determined by its brief history together with the usual signs of carcinoma in addition to the Roentgen ray and esophagoscopy study and, if necessary, biopsy findings.

Course and Duration. While the course of the disease is frequently rapid, it may progress slowly with periods of remission and, as a result of the healing of the ulcer, stricture may occur. The onset, however, is usually gradual, beginning with dyspepsia and finally with pain and dysphagia. In other instances, the ulcer remains latent until hemorrhage or perforation occurs. The duration of the disease is uncertain, varying from a few days to many years. In 63 per cent of Tilleston's cases it was under six months. The duration in our cases ranged between ten days and eight years. There can be but little question that clinical cure is often obtained; however, if death is not caused by perforation or hemorrhage incomplete healing may take place with the formation of esophageal stricture and dilatation. Death is usually due to perforation or hemorrhage but may be caused from inanition or from intercurrent diseases.

Treatment. Inasmuch as focal infections are known to play an important rôle in the etiology of peptic ulcerations all foci of infection should, as far as possible, be eradicated.

The treatment of uncomplicated peptic ulceration of the esophagus is mainly dietetic. An attempt should be made as far as possible to prevent further irritation and maintain rest. Milk as the special form of diet plays a most important rôle. It should be allowed exclusively for a week or ten days and in the very serious forms even as long as two or three weeks. It should be permitted only in small amounts given at frequent intervals. Following this, soft food may be allowed; always, however, in small quantities. Early in the course of the treatment olive oil may be administered. Alkalies should also be prescribed in the form of calcium carbonate,

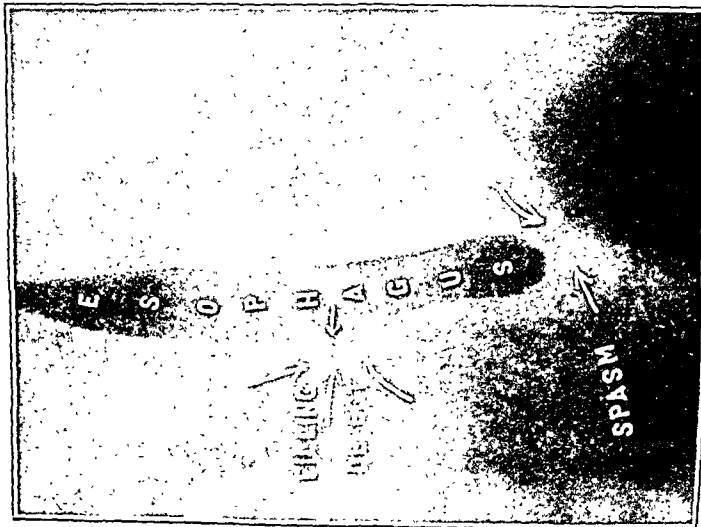


FIG. 1.—Illustrates a typical penetrating ulcer in the lower third of esophagus, on right posterolateral wall. The cardiac end shows definite spasm.

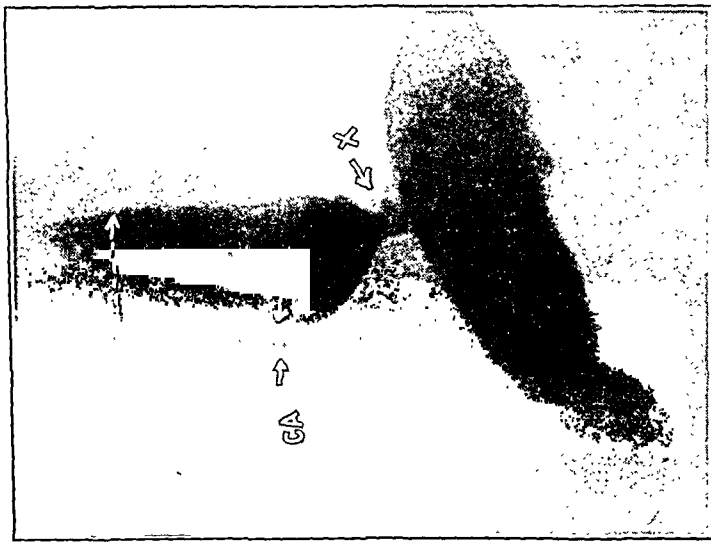


FIG. 2.—A dilated esophagus with obstruction due to carcinoma at the cardiac end involving the cardiac of the stomach. The right posterolateral wall above the obstructed area presents an ulcer defect which is carcinomatous.

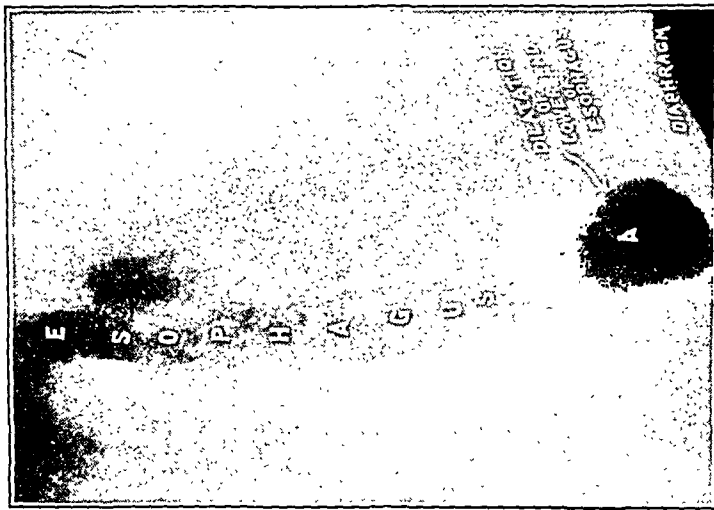


FIG. 3a.—Presents a large circumscribed dilatation at cardiac end, due to a chronic ulceration. (Oblique view.)

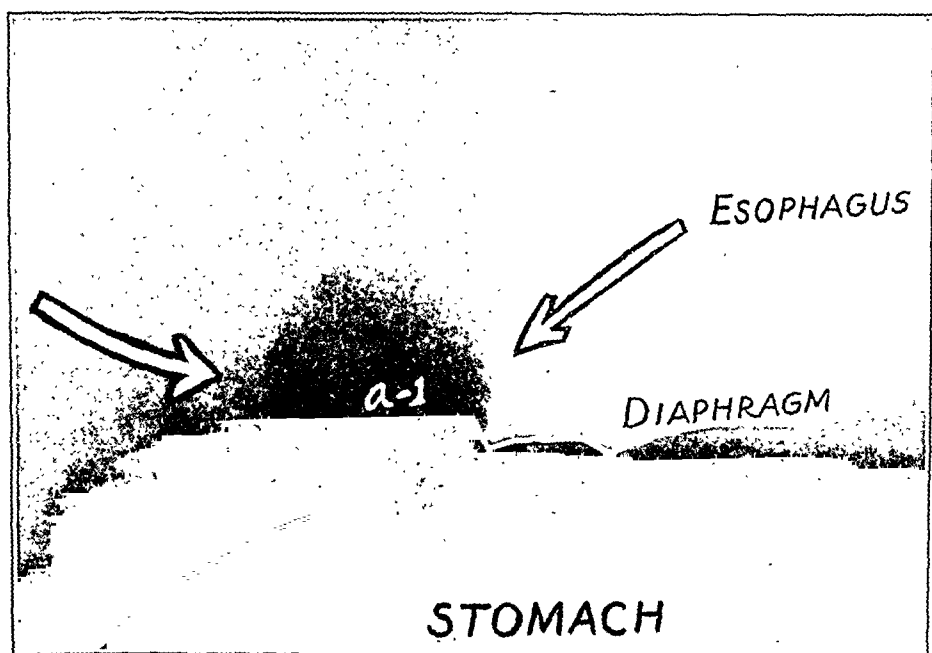


FIG. 3b.—Illustrates the same ulcer resembling a diverticulum or hernia of the cardia of the stomach through the esophageal opening. (Anterior view.)

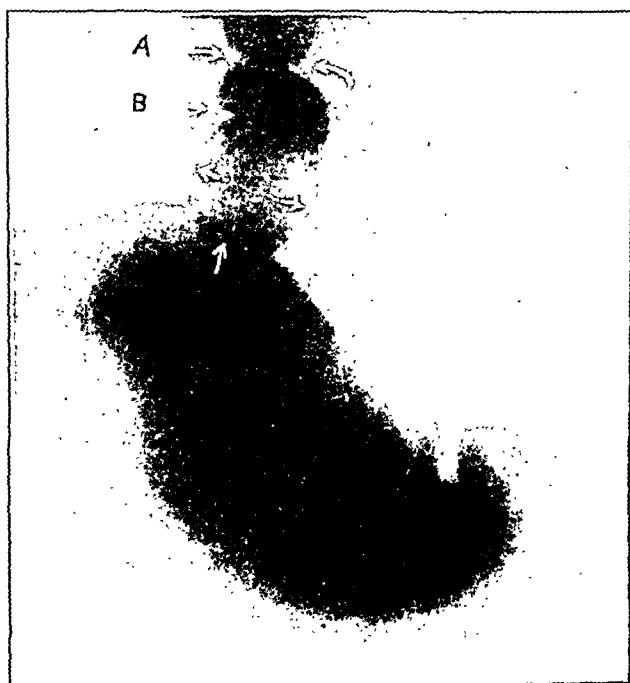


FIG. 4.—A slight dilatation in the lower third of esophagus with a constriction at A, and a small indentation on right lateral wall at B, the result of chronic ulceration.

sodium bicarbonate and bismuth subcarbonate. The last, especially in large doses, given at bedtime. Belladonna at times gives great relief, especially when spasm is present. In addition to the dietetic treatment in ulcerations of severe type, considerable relief may be afforded by direct application of various remedies through the esophagoscope. Relief from pain may be obtained at times by anesthetizing the ulcer with novocain or it may become advisable to cauterize the area with a solution of zinc chlorid, tincture of iodine or a solution of nitrate of silver, as has been recommended by Abram,²⁸ von Mikulicz³⁶ and others. Weiss⁴¹ and Sheehan³⁷ advise the introduction of the duodenal tube through the esophagoscope, which is to be retained for a period of from three to ten days and is to be utilized as a means of introducing nourishment. During the course of active treatment complete bedrest should be maintained.

If healing does not occur following the treatment already outlined gastrostomy should be performed. The esophagus can thus be placed at rest and nutrition may be fully maintained until complete healing has taken place. This operation was performed with success in the cases reported by Ewald,⁴² Tapia,⁴⁰ Dressman³⁵ and others.

Evidence of complete recovery is obtained by the disappearance of symptoms, absence of occult blood in the stools and if deemed advisable by means of a further esophagoscopy and Roentgen ray study. An absence of blood on the Einhorn string test will also afford additional evidence in this regard.

Of the 13 cases in our series, satisfactory relief was obtained in 8 instances by means of the simple dietetic and medical treatment outlined above. In 3 cases the local application of a 10 per cent solution of nitrate of silver in addition accomplished the desired result. One case remained unimproved and 1 died of perforation followed by pneumonia.

Conclusions. Although peptic ulcers of the esophagus are rare, they occur sufficiently often to be of clinical interest. They are usually observed in the lower third of the esophagus though occasionally they are located higher. These ulcers vary greatly in size and are usually single; the right posterolateral wall being most frequently involved. They resemble in many respects ulcers of the stomach and duodenum. Perforations are not uncommon. In large ulcerations, contraction takes place with the formation of stenosis and dilatation. In the small superficial ulcerations, healing is usual and the esophageal lesion is apt to be overlooked. The etiology of peptic ulcer of the esophagus is in every respect similar to that of the stomach and duodenum. In order that this affection may occur, it is necessary that the cardia remain patent so that the regurgitated acid gastric secretion may continue its corrosive effect upon the diseased area in the mucous membrane of the esophagus.

Ulcerations of the esophagus have been most frequently observed

in adults more commonly between the thirtieth and seventieth years and are found equally divided between males and females.

The most prominent symptoms of the disease are pain, dysphagia, vomiting, hemorrhage and perforation. There is often great difficulty in arriving at a diagnosis; however, this may be greatly aided by means of fluoroscopy and esophagoscopy. The treatment consists in the eradication of foci of infection, rest, the regulation of the diet and the administration of olive oil, alkalies and belladonna and at times by the direct application to the diseased area of various remedies such as a solution of nitrate of silver through the esophagoscope. If healing does not occur following this plan of treatment, gastrostomy should be performed to insure adequate feeding and the esophagus kept at rest for a considerable period of time.

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A STATISTICAL STUDY OF CLINICAL AND LABORATORY FINDINGS IN GASTRIC AND DUODENAL ULCER, WITH SPECIAL REFERENCE TO ROENTGENOLOGIC DATA.

BASED ON THE RECORDS OF 279 OPERATIVELY DEMONSTRATED CASES.

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Introduction. Gastric or duodenal ulcer has been demonstrated at operation in the hospital of the University of Pennsylvania during the past ten years on 279 patients. Many other individuals, diagnosed as having ulcer but not subjected to surgery, have been studied in the medical wards and the roentgenologic department. The present study was initiated with the idea of summarizing and correlating the important data on all the operatively proved cases, but as the work progressed it became apparent that some of the desired information was lacking in many of the records, and that, since under such circumstances each collection of statistical material would represent a different group of patients, it would be impossible to compare accurately the histories, the gastric analyses, the roentgenologic data and the operative findings. In consequence, it was decided to use the entire series only for certain special groups of data, such as the sex and age incidence and the duration of symptoms, and to select for the particular study of symptoms, signs and laboratory data only those cases on which the clinical records were very complete and on which the operative notes were reasonably satisfactory; this latter group includes 36 gastric and 100 duodenal cases. Though the number may be considered too small to have great statistical value, much is gained by the thoroughness with which each case has been studied and the accuracy with which the various groups of data may be compared.

Relative Incidence. The assembled data are presented in the accompanying tables and charts which are largely self-explanatory. Table I shows that the duodenal ulcer cases far outnumber the gastric ones (221 to 58) in the ratio of almost 4 to 1. This relationship is approximately that of the larger surgical clinics. In Moynihan's¹ series of 695 operated ulcer cases, reported in 1923, 531 were duodenal. Until recent years, textbooks stated that gastric ulcers outnumbered duodenal ones, but now almost all statistics quoted indicate the reverse condition and explain the error of former

compilations as due to faulty clinical diagnoses and to a failure of pathologists to examine carefully the duodenum for ulcers and scars. A recent publication by Sturtevant and Shapiro,² however, shows that in 7700 autopsies performed at the Bellevue Hospital between 1904 and 1922 more healed and unhealed gastric than duodenal ulcers (120 to 44) were found. The discrepancy between the necropsy and the operative data would seem to be due to the fact that a smaller number of the gastric lesions give rise to symptoms requiring surgical treatment. It is probable, indeed, that many of the gastric cases present no symptoms whatever, since in an analysis of the roentgenologic records, which more nearly represent the total number of patients with ulcer symptoms, Sutherland³ of the Mayo Clinic found an even greater preponderance of duodenal lesions (9 to 1).

TABLE I.—SEX OF ULCER CASES.

Sex.	Gastric.		Duodenal.		Two groups.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Male .	52	90	188	85	240	86
Female .	6	10	33	15	39	14
Total .	58	100	221	100	279	100

Sex Incidence. In the sex distribution, which is presented in the same table, it will be noted that 90 per cent of the gastric ulcers and 85 per cent of the duodenal ulcers occurred in men. The preponderance of duodenal ulcer in the male is well recognized, but it is commonly stated that gastric ulcer is more common in women. Although Moynihan,¹ in 164 gastric cases, had an equal distribution between the sexes, Balfour, in 1927, on the basis of the Mayo statistics stated that the sex incidence for the chronic cases was the same as for duodenal ulcer, about 4 to 1 in favor of males. Sturtevant and Shapiro in their autopsied cases found the ratio of men to women about 3 to 1 in each group. While the difficulty in diagnosis renders a decision as to sex distribution in the simple acute erosions or ulcers uncertain, the recent literature and our results suggest that of those coming to operation and seen at autopsy the great majority, both gastric and duodenal, is in the male sex.

Age Incidence. The age incidence for each ulcer group is presented in Tables II to V, which show, for the total series of 279 cases, not only the age at which they were referred to the hospital for study and treatment, but also that at which according to their histories ulcer symptoms first occurred. The actual figures and the percentages are given for the sexes separately and combined.

Three-fourths of the gastric cases (76 per cent) (Table II) were forty or more years of age at the time of admission, the majority of these (57 per cent or 43 per cent of the total number) being in the fifth decade of life; whereas only a half (52.9 per cent) of the duodenal cases (Table III) were aged forty years or over, and the numbers in the fourth and fifth decades were approximately the same (31.7 and

29.8 per cent). Furthermore, three-fourths of the gastric cases (Table IV) had their first digestive symptoms after the thirtieth year and more than 60 per cent of the duodenal cases (Table V). (See Chart I.)

TABLE II.—AGE INCIDENCE IN 58 GASTRIC ULCER CASES AT THE TIME OF ADMISSION TO HOSPITAL, BY SEX AND FOR THE TOTAL GROUP.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19 .	1	2	1	2
20 to 29 .	5	10	5	8
30 to 39 .	8	15	8	14
40 to 49 .	21	40	4	66	25	43
50 to 59 .	10	19	1	17	11	19
60 to 69 .	7	14	1	17	8	14
Total .	52	100	6	100	58	100

TABLE III.—AGE INCIDENCE IN 221 DUODENAL ULCER CASES AT THE TIME OF ADMISSION TO HOSPITAL, BY SEX AND FOR THE TOTAL GROUP.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19 .	1	0.5	1	0.5
20 to 29 .	31	16.5	2	6	33	14.9
30 to 39 .	60	31.8	10	30	70	31.7
40 to 49 .	57	30.4	9	28	66	29.8
50 to 59 .	30	16.0	11	33	41	18.5
60 to 69 .	8	4.3	8	3.6
70 to 79 .	1	0.5	1	3	2	1.0
Total .	188	100.0	33	100	221	100.0

TABLE IV.—AGE INCIDENCE IN 58 GASTRIC ULCER CASES AT THE TIME OF ONSET OF SYMPTOMS, BY SEX AND FOR THE TOTAL GROUP.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19 .	2	4	1	17	3	5
20 to 29 .	11	21	11	19
30 to 39 .	13	25	1	17	14	24
40 to 49 .	13	25	3	49	16	28
50 to 59 .	9	17	1	17	10	17
60 to 69 .	4	8	4	7
Total	52	100	6	100	58	100

TABLE V.—AGE INCIDENCE IN 221 DUODENAL ULCER CASES AT THE TIME OF ONSET OF SYMPTOMS, BY SEX AND FOR THE TOTAL GROUP.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10 to 19 .	12	6.4	2	6	14	6.3
20 to 29 .	66	35.1	6	18	72	32.6
30 to 39 .	58	30.8	11	34	69	31.2
40 to 49 .	31	16.5	10	30	41	18.5
50 to 59 .	11	5.9	3	9	14	6.3
60 to 69 .	6	3.2	1	3	7	3.2
?	4	4	1.9
Total .	188	100.0	33	100	221	100.0

Considering next the age distribution according to sex it will be observed, for both the gastric and the duodenal groups, that the men

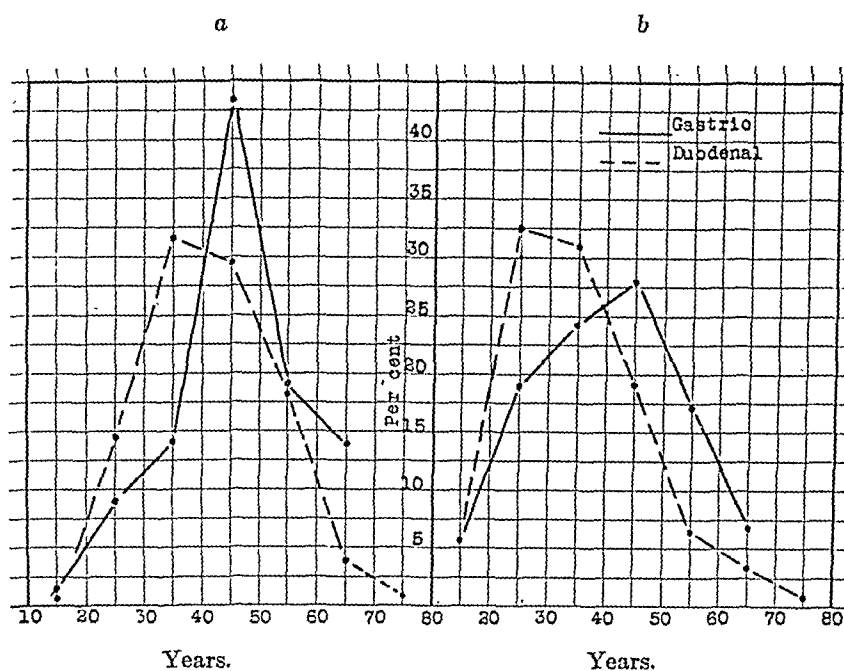


CHART I.—(a) Age of gastric and duodenal ulcer cases at time of admission to hospital (58 and 221 cases respectively). (b) Age at onset of symptoms in same cases of gastric and duodenal ulcer.

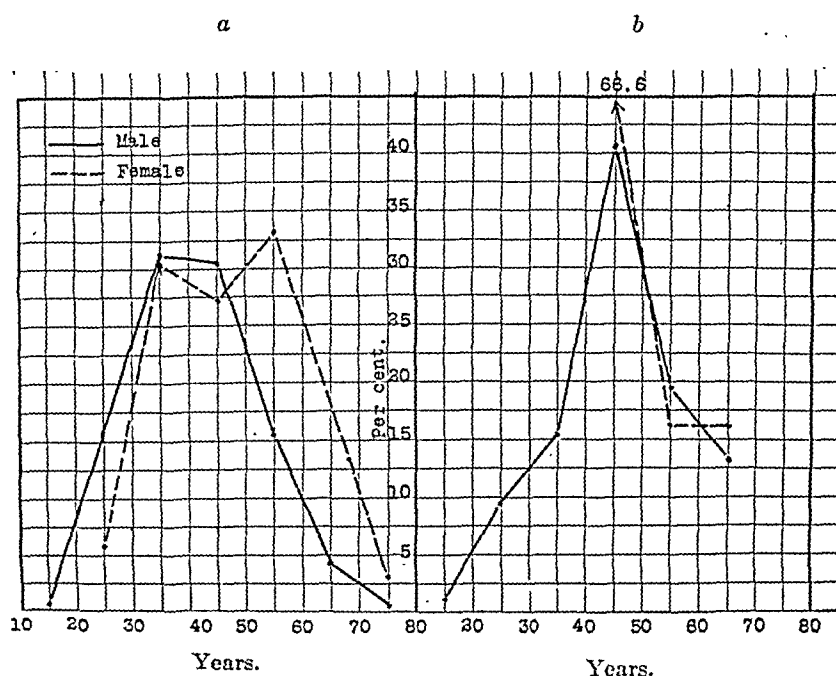


CHART II.—(a) Age of male and female duodenal ulcer cases at the time of admission to the hospital (188 and 33 cases respectively). (b) Age of male and female gastric ulcer cases at the time of admission to the hospital (52 and 6 cases respectively).

were younger both for the time of hospitalization and for the onset of symptoms. For the admission time, all the women with gastric lesions and 64 per cent of those with duodenal lesions were forty or more years of age against respectively 73 per cent of the men with gastric lesions and 51.2 per cent of those with duodenal lesions. For the time of onset of symptoms, the corresponding figures for the women were 66 per cent gastric and 42 per cent duodenal against 50 and 26 per cent respectively for the men. (See Chart II.)

These results find surprisingly little support in even recent textbooks, chiefly because it is still common practice to quote and be guided by statistics compiled years ago on the basis of autopsy findings and of unproved clinical diagnoses. C. F. Martin in Osler's System⁴ says that gastric ulcer is most common between twenty and thirty years of age and that the average age for males is 36.7 years and for females 27.1 years. His combined statistics on 704 cases showed 37 per cent in the third decade and 26.5 per cent in the fourth. Speaking specifically of duodenal ulcers he says that they are commonest in the third decade. Aaron,⁵ in 1927, speaking of both gastric and duodenal cases, says that in women the period of liability was noted to begin earlier than in men and to reach its maximum at twenty-five to thirty years. Crohn,⁶ in the same year, while admitting that ulcer more commonly becomes a clinical problem in the later decades states that its onset can be traced in over half the cases to the period between ten and thirty years of age and that gastric ulcer is more common in younger persons and duodenal ulcer of greater frequency in older individuals. In so doing, he overlooks Gruber's statistics, which he himself quotes, showing 60 per cent of gastric ulcers to occur between forty and seventy years of age. He also gives Fenwick's statement of 1900 to the effect that three-fourths of the cases in females begin before the thirtieth year. Friedenwald,⁷ in 1912, in an analysis of 1000 gastric and duodenal cases found the acme of incidence in the third decade, but his cases were not proved. On the other hand, Moynihan,⁸ in the same year, analyzing 187 proved duodenal cases found the majority of them in the fourth and fifth decades and Blackford and Dwyer,⁹ in a recent paper covering 332 cases found the average age at the time of diagnosis to be forty-one years for duodenal ulcer and forty-eight for gastric ulcer; they found 66 per cent of the former group seeking relief before forty-five years of age and only 33 per cent of the latter.

Symptoms. *Pain.* The outstanding and almost universal symptom of peptic ulcer is upper abdominal pain and in Table VI are given the terms used by our patients to describe the nature of the pain from which they suffered. Not infrequently several adjectives were employed in a single case: each has been recorded, and the totals for the vertical columns are, therefore, greater than the number of cases studied. It is interesting to note that, with the

exceptions of "burning" and "gnawing," the adjectives occurred with almost equal frequency in the two groups. These exceptions, however, would seem to be of significance, since the term "burning" appears five times more often in the gastric series and "gnawing" only in the duodenal group. If burning pain indicates, as Hurst has claimed, acid regurgitation into the esophagus our findings would suggest that this happens much more often in cases of gastric ulcer. Gnawing pain is often attributed to overactive gastric peristalsis and yet only 5 of our 18 duodenal ulcer cases with this type of distress had hyperperistalsis on fluoroscopic examination, and only 8 had a residue of the barium meal after six hours; high acidity of the gastric contents was the condition most frequently associated (14 of the 18 cases). Severe pain occurred in almost one-third of each group and was associated with high gastric acidity in three-fourths of the cases; and with pyloric stenosis and adhesions, each, in one-half.

TABLE VI.—NATURE OF THE PAIN IN ULCER CASES.

Descriptive term used by patient.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases). No. and per cent.
	No.	Per cent.	
Severe	11	31	28
Dull	7	19	28
Sharp	9	25	18
Gnawing	18
Burning	14	39	8
Cutting	5
Boring	4
Aching	1	3	5
Colicky	4
Sense of fullness	1	3	3

TABLE VII.—LOCATION OF PAIN IN ULCER CASES.

Location.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases). No. and per cent.
	No.	Per cent.	
Epigastrium	28	78	92
Back	7	19	15
Right hypochondrium	4	11	2
Left hypochondrium	3	8	7
Lower abdomen	1	3	3
Left chest	2	6	
Shoulder	2

The location of the pain (Table VII) was usually, as is generally recognized, in the epigastric region (78 per cent for the gastric series and 92 for the duodenal). Of the 7 gastric ulcer cases having pain in the back, usually associated with epigastric pain, 4 had deeply penetrating lesions, 2 involving the lesser curvature and the other 2 the posterior wall of the stomach near the lesser curvature. Two others had indurated posterior wall ulcers, but the seventh was a gastroduodenal ulcer case without, so far as the records indicate, any involvement of the posterior wall. Of the 15 duodenal cases

with back pain 1 had an adhesion of the ulcer area to the pancreas, 2 had adhesions to the posterior wall of the abdomen, 2 others had gastric adhesions, a sixth one presented fibrous connection with the gall bladder, and a seventh and an eighth, adhesions about the appendix and duodenum, respectively: others, though specific adhesions were not mentioned, had old indurated ulcers that had existed for from two to ten years. It is quite probable that some of these also had posterior connections. One other case with back pain should be referred to as it was our only instance of ulcer in the second part of the duodenum; another was at the junction of the first and second parts. It would appear, therefore, that when an ulcer patient complains of referred pain in the back the probabilities are that the ulcer is an old one and that there exist adhesions to structures posterior to the stomach. The occasional complaint of right or left upper quadrant pain did not seem to have significance, though of the 2 gastric cases having left chest pain the lesions were high on the lesser curvature and 1 was of the deeply penetrating type.

TABLE VIII.—TIME OF PAIN IN ULCER CASES.

Time in relation to meals.	Gastric ulcer.		Duodenal ulcer. No. and per cent.
	No.	Per cent.	
Immediately after	5	14	2
Within one-half hour after	1	3	1
One-half to one hour after	3	8	8
One to two hours after	9	25	12
Two to three hours after	1	3	29
Three to four hours after	2	6	15
<hr/>			
No relation	11	30	13
Not stated	4	11	30
<hr/>			
Total	36	100	100

Table VIII shows that in most instances a fixed time relation of the pain to meals existed, but that the interval between the ingestion of food and the onset of the pain varied considerably. In a large way it may be pointed out that the gastric lesions tended to give a shorter interval than the duodenal ones (the largest percentage of those in which a relationship existed having a period of one or two hours against a period of two or three hours for the duodenal cases). It has been stated that the higher the lesion in the stomach the sooner the pain after food, but our data do not lend support to this idea and, furthermore, it is difficult to explain the time variation in the duodenal cases on such a basis. Of those having no food-pain relationship the majority was gastric: this cannot be explained on the basis of gastric retention since a gastric residue six hours after a barium meal occurred with about equal frequency in the two groups.

Various factors give temporary relief from the pain caused by these ulcers but the ingestion of food was the most frequent factor

in our series (36 per cent for the gastric group and 57 per cent for the duodenal group), as showed in Table IX. The administration of alkalis was next most effective in each group. This relief undoubtedly comes as a result of neutralizing the acid gastric contents, but whether such neutralization acts by lessening direct chemical irritation of the ulcer area or by decreasing peristalsis and local spasm is not settled. This is a problem which we plan to investigate by means of simultaneous fluoroscopic observation and chemical studies on gastric and duodenal contents. Vomiting also probably acts as a means of relieving pain by ridding the stomach of the stimulating material.

TABLE IX.—FACTORS PRODUCING RELIEF OF PAIN IN ULCER CASES.

Factor.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases). No. and per cent.
	No.	Per cent.	
Ingestion of food	13	36	57
Administration of alkalis	8	22	44
Vomiting	9	25	23
Pressure	1	3	2
Eructations	3	8	
Catharsis	1	3	2

TABLE X.—FREQUENCY OF PHENOMENA OTHER THAN PAIN IN ULCER CASES.

Phenomenon.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases). No. and per cent.
	No.	Per cent.	
Vomiting	27	75	68
Eructations	21	58	64
Nausea	12	33	35
Hematemesis	15	42	19
Appetite:			
Good	10	28	29
Poor	13	36	11
Not stated	13	36	60
Bowels:			
Constipated	17	47	56
Diarrhea	1	3	6
Normal	10	28	20
Not stated	8	22	18
Periodicity of symptoms	22	61	64

Other Symptomatic Phenomena. All of the phenomena referred to in Table X have some bearing on diagnosis when considered in connection with characteristic pain and other special diagnostic findings, but, with the exception of hematemesis, have far less significance than has pain itself. Vomiting, eructations and nausea are present in so many gastric and even extragastric conditions that their presence alone or combined means little or nothing. Fortunately they occur rarely in ulcer cases without associated pain. Macroscopic blood in the vomitus is of great importance and should always suggest the possibility of ulcer even when there are no other

symptoms. It will be noted that 42 per cent of the gastric cases and 19 per cent of the duodenal ones showed it; this figure for the gastric series would probably be lower in a larger series, since in the Mayo cases for 1921 and 1922 (1072 cases) only about one-fifth of each group showed gross hemorrhage. The appetite was more often impaired in the gastric than in the duodenal cases, for which we have no explanation since retention occurred with equal frequency in the two groups. Our figures support the general opinion that ulcer patients are frequently constipated, but the percentages are not greater perhaps than for hospital cases as a whole. Periodicity of symptoms is of considerable diagnostic importance. By this term is meant the presence of characteristic symptoms over periods of months with intervening periods of months or even years in which no such symptoms are manifest. It will be noted that it occurred in each group, and with about the same degree of frequency.

TABLE XI.—NUMBER AND PERCENTAGE OF ULCER CASES THAT PERFORATED, BY DECADES AND FOR THE TWO GROUPS.

Decade.	Gastric cases.			Duodenal cases.		
	Total No.	No. perforating.	Per cent perforating.	Total No.	No. perforating.	Per cent perforating.
10 to 19 .	1	1	100	1	1	100
20 to 29 .	5	3	60	33	5	15
30 to 39 .	8	2	25	70	8	16
40 to 49 .	25	3	12	66	7	11
50 to 59 .	11	2	18	41	6	15
60 to 69 .	8	0	0	8	4	50
70 to 79	2	0	0
Total	58	11	19	221	31	14

Incidence of Perforation. Perforation occurred in 42 of our series of 279 cases (15 per cent): 11 of the gastric group (19 per cent) and 31 of the duodenal (14 per cent) (Table XI). No special decade of life showed a preponderance of these: 19, 24, 24 and 19 per cent occurring respectively in the third, fourth, fifth and sixth ten-year periods. These figures are in agreement with those of Dunbar¹⁰ who, in a large series of 387 perforating cases, found 21.9, 29.2, 20.6 and 17.2 per cent in the same respective decades. Of the ulcer cases occurring in each decade, the percentage that perforated is showed in the table. It will be noted that each of the 2 cases under twenty years of age perforated, that the next highest percentage for the gastric cases was in the third decade, that the frequency of perforation for the duodenal cases for the third, fourth, fifth and sixth decades was about the same, and that 4 of the 10 cases in the seventh and eighth decades (40 per cent) perforated. Table XII shows that in 2 of our gastric cases and in 5 of the duodenal ones perforation occurred without a preceding history of digestive trouble, but all the others gave such a history, though symptoms had been present in most of the gastric cases less than a year.

TABLE XII.—DURATION OF DIGESTIVE SYMPTOMS IN ULCER CASES THAT PERFORATED (IN TOTAL SERIES OF 279 CASES).

Time.	Gastric. Number.	Duodenal. Number.
None before perforation	2	5
One month or less	2	7
Two to eleven months	4	1
One to two years	5
Three to four years	6
Five to nine years	5
Ten years or more	3	2
Total	11	31

TABLE XIII.—DURATION OF SYMPTOMS BEFORE ADMISSION TO HOSPITAL IN 279 ULCER CASES.

Time.	Gastric.		Duodenal.	
	No.	Per cent.	No.	Per cent.
None before perforation	2	3	5	2
One month or less	5	9	14	6
Two to eleven months	8	14	19	9
One to two years	13	22	36	16
Three to 4 years	5	9	32	15
Five to nine years	12	21	53	24
Ten to fourteen years	6	10	27	12
Fifteen or more years	6	10	31	14
Not stated	1	2	4	2
Total	58	100	221	100

Duration of Symptoms: The duration of symptoms in the total series of 279 ulcer cases (Table XIII) is similar for the two groups, and the variation in the time is striking. The ones showing no preceding digestive symptoms were admitted because of perforation. Approximately a fourth of the gastric and a sixth of the duodenal cases had been troubled for less than a year. More than 10 per cent of each group had had symptoms for fifteen or more years and a few stated that they had always had spells of indigestion.

TABLE XIV.—PHYSICAL FINDINGS IN ULCER CASES.

Positive finding.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases).
	No.	Per cent.	No. and per cent.
Spot of tenderness	21	57	38
Muscular rigidity	5	14	7
Palpable mass	3	8	4
Visible peristalsis	2	6	5
Oral sepsis	21	57	?

Physical Examination. Although Moynihan states that an accurate diagnosis of peptic ulcer may be made without a physical examination, Table XIV shows that 57 per cent of our gastric and 38 per cent of our duodenal cases had a definite spot of epigastric tenderness. Such a finding, together with a suggestive history, is

frequently of diagnostic aid, but it may occur in the absence of ulcer. When, in addition, there is muscular rigidity or a palpable mass or visible gastric peristalsis the physical examination becomes of great importance. In 1 of our cases with a palpable mass an old duodenal ulcer with calcified glands about it was found; another had an old healed ulcer with adhesions producing a diverticulum of the duodenum; others with a mass had no unusual findings at operation but Roentgen ray study showed pylorospasm and this doubtless produced the mass that was felt. Two of the gastric cases with muscular rigidity had deeply penetrating ulcers. The cases with visible peristalsis, with a single exception, had pyloric stenosis or spasm with gastric retention.

TABLE XV.—GASTRIC RETENTION IN ULCER CASES (THOSE HAVING SIMPLE TEST MEAL).

Amount of contents 45 to 60 minutes after test meal.	Gastric ulcer (16 cases).		Duodenal ulcer (47 cases).	
	No.	Per cent.	No.	Per cent.
Less than 100 cc.	6	38	13	28
100 to 200 cc.	5	32	19	40
200 to 300 cc.	2	12	7	15
300 to 400 cc.	1	6	4	9
400 to 500 cc.	1	6	2	4
500 to 600 cc.	1	6	2	4
Total	16	100	47	100

Gastric Analysis. During recent years our patients have been given fractional test meals routinely and in consequence only the earlier ones, whose total gastric contents were removed forty-five minutes to one hour after ingestion of the Ewald meal, could be used in the preparation of Table XV. The amounts obtained at that time have been grouped; and, if we consider, as is usually done, a quantity over 100 cc. as indicative of gastric retention, it will be observed that 62 per cent of the gastric cases showed retention and 72 per cent of the duodenal ones. An almost equal percentage showed, by fluoroscopic examination, a moderate to marked residue of the barium meal after six hours. It is our belief that such a simple total removal of the gastric contents forty-five minutes to one hour after the administration of an Ewald meal is as satisfactory a method of showing the degree, if any, of gastric retention as is the usual roentgenologic study.

Table XVI gives the maximal free hydrochloric acid concentration and total acidity of the gastric contents after Ewald meals in 30 of the gastric and 83 of the duodenal cases. In the others it had not been considered safe to introduce a gastric tube. Forty-six per cent of the gastric cases had free hydrochloric acid figures (20 to 39) that are within so-called normal limits, whereas 41 per cent had what has by some been considered hyperchlorhydria. Only 1 case had no free hydrochloric acid. All the duodenal cases had some free acid, but

in 7 per cent it was below normal; on the average the acidity in these cases was higher than for the gastric group. Rehfuß¹² found the total acidity in excess of 70 in 38 per cent of his series of gastric ulcer cases, but he also found that 40 to 45 per cent of supposedly normal individuals had a concentration higher than that. Bennett and Ryle¹³ in a series of 100 healthy men found some free acid concentrations as high as 100 and concluded that a high acid figure cannot in itself be regarded as a pathologic finding. Bell¹⁴ in 24 gastric ulcer cases found the acidity low in 33 per cent, intermediate in 21 and high in 46; in 34 duodenal ulcers he found the respective percentages to be 12, 9 and 79. Moynihan¹ in 39 gastric ulcer cases

TABLE XVI.—FREE HYDROCHLORIC ACID CONCENTRATION AND TOTAL ACIDITY OF GASTRIC CONTENTS IN ULCER CASES (HIGHEST FIGURES WHEN FRACTIONALS DONE).

Amount required to neutralize 100 cc. N/10 NaOH.	Gastric ulcer (30 cases).				Duodenal ulcer (83 cases).			
	Free HCl.		Total acidity.		Free HCl.		Total acidity.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
0	1	3						
10 to 19 cc.	3	10	1	3	6	7		
20 to 29 cc.	7	23	7	8	1	1
30 to 39 cc.	7	23	1	3	13	16	6	7
40 to 49 cc.	8	27	5	17	14	17	4	5
50 to 59 cc.	1	3	6	21	17	21	6	7
60 to 69 cc.	2	7	7	23	6	7	15	18
70 to 79 cc.	7	23	12	14	14	17
80 to 89 cc.	1	4	1	4	5	6	8	10
90 to 99 cc.	2	7	3	4	12	15
100 to 109 cc.	6	7
110 to 119 cc.	6	7
120 to 129 cc.	2	3
150 to 159 cc.	3	3
Total	30	100	30	100	83	100	83	100

found intermediate acidity in 34.2 per cent and high acidity in only 20.9 per cent; whereas in 71 duodenal cases he found 72.7 per cent to have high acidity. Rehfuß in 100 cases of duodenal ulcer got a high acid curve in 78 per cent and Ryle¹⁵ quotes figures which show 70 per cent of chronic duodenal ulcers with high acidity and 30 per cent with intermediate acidity; none with low acidity and achlorhydria. Our data, together with those quoted, would seem to indicate a tendency toward high acidity in both gastric and duodenal ulcer, greater in the latter, and yet gastric ulcer may occur with no free hydrochloric acid and duodenal ulcer only rarely, if ever, has an acid concentration greater than may be found in certain presumably healthy persons.

ROENTGENOLOGIC CONSIDERATIONS.

BY EUGENE P. PENDERGRASS, M.D.

TABLE XVII gives the roentgenologic findings under six headings. The type of stomach has been divided roughly into three classes, the grouping being made with regard to the position of the stomach rather than the tone. A level corresponding to the upper limits of the crests of the ilia has been used arbitrarily as the dividing line. Any stomach that had the greater curvature on the level with the crests of the ilia was regarded as the fish-hook type, above steer horn and below ptotic, the films being made in the erect posture.

TABLE XVII.—ROENTGENOLOGIC FINDINGS IN ULCER CASES.

Roentgenological finding.	Gastric ulcer (36 cases).		Duodenal ulcer (100 cases).	
	No.	Per cent.	No. and per cent.	
Anatomic type of stomach	Fish-hook	15	42	64
	Steer-horn	6	17	14
	Ptotic	13	36	19
	Not stated	2	5	3
Residue of barium meal in stomach after six hours	Slight	3	8	21
	Moderate	6	17	19
	Marked	13	36	17
	Complete	4	11	3
	None	9	25	36
	Not stated	1	3	4
Type of gastric peristalsis	Hyperperistalsis	21	59	65
	Hypoperistalsis	8	22	15
	Normal	5	14	15
	Not stated	2	5	3
	Hypermotility	20	55	51
Degree of gastric motility	Hypomotility	14	39	26
	None	5
	Normal	1	3	15
	Not stated	1	3	3
Pyloric spasm	Present	17	48	30
	Absent	8	22	53
	Uncertain	3	8	6
	Not stated	8	22	11
Constant defect in films	Present	31	86	92
	Absent	5	14	6
	Not stated	2

The table shows that both the gastric and the duodenal ulcers occurred most frequently in the fish hook, or prevailing type of stomach, the second in frequency being in the ptotic variety. This data is probably of no significance except in correcting an impression of ours; that the ulcers would probably be found most frequently in the ptotic variety of stomach because of the mechanical factor of decreased motility with subsequent decreased tonicity. The position of the stomach is probably of no significance, therefore, if one is justified in drawing conclusions on such a small series of cases.

The amount of residue as indicated in the table is self-explanatory.

It will be noted that a residue occurred in 26 (72 per cent) of the gastric cases and 60 (60 per cent) of the duodenal group. The causes of residue in the gastric cases were as follows: 15 gave evidence of pylorospasm, 4 had organic obstruction, and in 7 we found no specific explanation.

Of the duodenal cases (60) showing retention after six hours, 23 showed pylorospasm and 20 organic obstruction; no explanation can be given for the residue in the other 17 cases. Our finding of 60 per cent with gastric residue is greatly in excess of that reported by Carman¹⁶ who in larger series of 417 duodenal ulcer cases observed that a residue occurred in 25 per cent. If, however, the 11 cases of pyloric stenosis and the 9 cases of gastroduodenal ulcer are excluded, the percentage showing retention is reduced to 40, and this approximates the figures given by other observers.

The type of gastric peristalsis, whether normal, excessive or subnormal, has been based on the activity of the stomach as disclosed after a ten to fifteen minute fluoroscopic examination. No attempt is made to further subdivide these groups, although every roentgenologist recognizes at least various subtypes of hyperperistalsis and we have observed them. Fifty-nine per cent of the gastric and 65 per cent of the duodenal cases showed some form of excessive peristalsis. In the group of gastric ulcers, the waves were either interrupted at the site of the ulcer or they began below it. Continuous waves of hyperperistalsis were more often noted in the gastric group and paroxysmal waves of hyperperistalsis with intermittent periods of inactivity were more frequently observed in the duodenal ulcer series. Antiperistalsis was noted in a few cases of extreme pylorospasm and stenosis. Hypoperistalsis was noted in stomachs that had very little tone in both groups; in the duodenal group it occurred more often in the lesions with which there was an associated marked residue. Not infrequently these lesions had been present for a long time, possibly accounting, therefore, for the lack of tone.

By gastric motility is meant the passage of stomach contents into the duodenum and the term has no reference to peristaltic activity. Hypermotility was observed in 20 (55 per cent) gastric, and 51 (51 per cent) duodenal cases. The former figure is surprising since it is generally assumed that hypermotility does not occur in the presence of pylorospasm. In our gastric cases 48 per cent had pylorospasm, as against 30 per cent in the duodenal group. More careful analysis reveals, however, that of the 20 gastric cases 6 had definite pyloric spasm at some time during the fluoroscopic examination. It must be admitted, therefore, that hypermotility, as we interpret it, can occur when spasm of the pylorus is present. In the 6 cases with pylorospasm and hypermotility 4 ulcers were located on the lesser curvature and 1 was on the greater curvature but 1 was a small ulcer near the pylorus. The relatively low percentage (51) of hypermotility in the duodenal group is to be explained by the fact

that we included 20 cases with organic pyloric obstruction. Exclusive of these and of those in which no statement of motility is made, hypermotility occurred in 66 per cent and normal motility in 20 per cent. In the 14 gastric cases having hypomotility, 10 had pyloric spasm, 3 had organic stenosis at operation and the other a large sclerosing ulcer near the cardia.

Pyloric spasm, presumably a reflex phenomenon from gastric ulceration, was present in only 17 (48 per cent) of our gastric cases. This figure is less than anticipated, and occurred most often when the lesion was near the pylorus (13 of the 17 cases); in 3 cases the ulcer was on the lesser curvature and in 1 on the greater. When definitely stated that no spasm was present, the lesion was high on the lesser curvature except in two instances in which the gastric ulcer reached the pyloric ring (gastroduodenal ulcers). If the cases in which no statement of spasm was made, and in which it was uncertain, are excluded, pylorospasm occurred in 68 per cent of the gastric series. Calculating in the same way 36 per cent of the duodenal cases showed pylorospasm and in these the ulcer was found just distal to or at least very near the pyloric ring.

A great deal of diagnostic importance has been placed on the presence or absence of a constant filling defect in the films of the above series of cases. Only 11 cases, 5 gastric (14 per cent) and 6 (6 per cent) duodenal out of the entire series failed to show such a defect. Pancoast¹⁷ has always laid a great deal of stress upon a routine which consists of a fluoroscopic and a roentgenographic study. For instance, a deformity of the stomach or duodenum appearing in the films may be due to a number of lesions, and without a fluoroscopic examination one hesitates to make a differential diagnosis. Likewise, fairly typical fluoroscopic phenomena cannot be regarded as entirely diagnostic without a filling defect. It is true that one not infrequently ventures the opinion of a nondeforming ulcer, yet such a diagnosis cannot be accepted as readily as if there were a small defect present. The filling defect itself may be and usually is due to a small lesion plus spasm or adhesions, except when there is definite cicatrization present.

The roentgenologic diagnoses and the operative findings in the 36 gastric ulcer cases are presented in Table XVIII. It is felt that with the exception of the 2, in which the stomach was said to be negative, these diagnoses may be accepted as correct (94 per cent). Both of the errors occurred in the patients who had very small ulcers on the lesser curvature and in 1 of these, because of extreme anemia following a gastric hemorrhage, the examination had not been complete. It is at times impossible for the roentgenologist to state with certainty whether a gastric deformity is due to ulcer or adhesions, but usually his demonstration of the filling defect alone is sufficient, when the clinical history is taken into consideration, to establish the exact diagnosis. This is our justification for including

as correct the 4 cases reported as ulcer or adhesions. The definite determination of pyloric stenosis is considered a diagnosis in itself, justifying operation no matter what its cause, and the roentgenologist cannot be expected, in the usual case, to go further.

TABLE XVIII.—ROENTGENOLOGIC DIAGNOSES IN 36 PROVED GASTRIC ULCER CASES.

Diagnosis.	No.	Operative findings.
Ulcer of the lesser curvature	19	Seventeen on lesser curvature, 2 on posterior wall near pylorus.
Gastric ulcer, location not stated	4	One on posterior wall, 1 on lesser curvature, 1 on greater curvature, location of other not stated.
Gastric ulcer or adhesions	4	One on lesser curvature, 1 near pylorus, location of others not stated.
Pyloric obstruction	3	All showed stenosis associated with gastric ulcer.
Gastric ulcer or subtotal gastrectomy	1	Large ulcer on lesser curvature near pylorus with adhesions.
Gastric ulcer, probably on posterior wall	1	On posterior wall near greater curvature.
Gastric ulcer at pylorus with crater	1	Confirmed.
Gastric ulcer or carcinoma	1	On lesser curvature.
Stomach negative	2	Both showed ulcer on lesser curvature, one being very small.

Diagnosis correct in 94 per cent of cases.

TABLE XIX.—ROENTGENOLOGIC DIAGNOSES IN 100 PROVED DUODENAL ULCER CASES.

Diagnosis.	Number and per cent.	Special operative findings.
Duodenal ulcer	15	Confirmed.
Duodenal ulcer probably	13	All ulcers.
Duodenal ulcer or adhesions	29	All ulcers.
Duodenal ulcer and adhesions	7	Confirmed.
Duodenal adhesions	3	One healed, 1 very small ulcer, 1 ulcer and adhesions.
Duodenal adhesions probably	6	Three healed, 1 at junction first and second portions, 1 small on anterior wall, 1 large on posterior wall.
Duodenum uncertain because it was not shown on films	2	One large stellate, first portion; 1 small, indurated, near pylorus.
Duodenum negative	1	Ulcer of second part of duodenum.
Pyloric ulcer	4	Two were pyloric; 2 duodenal.
Pyloric stenosis	11	Two ulcers at pylorus, 9 beyond it.
Gastroduodenal ulcer	9	One was typically pyloric; 8 on duodenal side.
Total	100	
Diagnosis practically correct	88	
Diagnosis missed	12	

In the duodenal group analyzed in Table XIX there are several diagnoses that should be discussed. Three cases were diagnosed duodenal adhesions and 6 probable duodenal adhesions. In these 9 cases, the films showed an inconstant filling defect, and there was an absence of fluoroscopic phenomena that would suggest an ulcer.

It is rather interesting to note that 4 of these cases had healed ulcers. Possibly one should make a diagnosis of ulcer or adhesions with the majority of evidence in favor of one or the other. This seems logical when we appreciate that the major portion of a given filling defect may be spasm or spasm plus adhesions.

In the group "duodenum uncertain because it was not shown on films" the fluoroscopic phenomena were not typical and the examination should have been repeated, but the clinical phenomena were suggestive enough to justify operation without additional confirmatory evidence.

One case was diagnosed "duodenum negative," and at operation an ulcer was found in the second portion of the duodenum. Fortunately, ulcers occur in the second portion very rarely,¹⁶ and when they do one can occasionally make the diagnosis by the fluoroscopic phenomena. Direct evidence of the ulcer cannot be obtained in the second portion because of the rapid motility. The duodenal bulb is the only part in which there is a normal stasis.¹⁶

TABLE XX.—MORE COMPLETE ROENTGENOLOGIC DIAGNOSIS AND OPERATIVE FINDINGS IN 11 PROVED DUODENAL ULCER CASES LISTED UNDER HEADING OF PYLORIC STENOSIS IN TABLE.

No. of case.	Roentgenologic diagnosis.	Operative findings.
19	Pyloric stenosis, with 18 hour retention. No filling of duodenal cap.	Old crater-like ulcer with annular contraction 1 inch beyond pylorus.
33	Pyloric obstruction. Ulcer or secondary carcinoma of stomach (?)	Large callous ulcer 1 inch beyond pylorus.
41	Pyloric stenosis due to ulcer or carcinoma.	Duodenal ulcer producing complete obstruction.
63	Pyloric obstruction with spasm. Duodenum uncertain due to lack of filling.	Ulcer of first part of duodenum with adhesions.
66	Pyloric obstruction with dilatation; cause uncertain; 48-hour retention.	Dilated and atonic stomach. Ulcer on anterior wall of duodenum near pylorus.
70	Pyloric obstruction with gastric dilatation. Duodenum probably negative.	Ulcer of first part of duodenum.
75	Pyloric obstruction with spasm. No visible ulcer. Duodenum uncertain due to lack of filling.	Small ulcer at pylorus.
93	Pyloric obstruction.	Large indurated ulcer $\frac{1}{2}$ inch beyond pylorus.
106	Pyloric obstruction: carcinoma, ulcer or adhesions.	Old indurated ulcer of duodenum.
125	Pyloric stenosis. No filling defect due to stenosis.	Callous duodenal ulcer.
143	Pyloric stenosis. Pyloric ulcer. Duodenum uncertain.	Ulcer of pylorus.

The diagnosis of "pyloric stenosis and gastroduodenal ulcer" was made on 20 occasions in this group and of these 17 cases had the pathology on the duodenal side. The gastroduodenal ulcer is

possibly an earlier stage of pyloric stenosis when one gets enough filling of the duodenal bulb to show the defect and its extension to the pylorus. This ulcer may ultimately cause obstruction from either cicatrization, spasm, or both. Pyloric obstruction is essentially an entity and will always remain so and the patient is operated upon to relieve the obstruction.

To summarize the findings in Table XIX one will note that the diagnosis was essentially correct in 88 instances, and missed in 12. Of the 12 cases, 4 had healed ulcers, 2 definitely active ulcers and 2 in which the duodenum was not shown, and finally there was 1 case in which there was no filling defect in the duodenal bulb but an ulcer was found in the second portion.

Table XX referring to the 11 pyloric stenosis cases does not need any further comment.

Summary and Conclusions. The clinical and laboratory data on 279 operatively proved gastric and duodenal ulcer cases, representing a ten-years' experience in this hospital, are analyzed, especial attention being given to a selected group of 36 gastric and 100 duodenal cases. The duodenal outnumbered the gastric cases in the ratio of 4 to 1, and it is pointed out that for all of those presenting symptoms the duodenal preponderance is even greater. The male sex predominated in each group (85 to 90 per cent) and the women were on the average a little older than the men. Aside from the roentgenologic findings, the history was of greatest diagnostic importance and sometimes afforded evidence suggesting the gastric or duodenal localization of the lesion. The physical examination was of less diagnostic importance, although the finding of a small spot of epigastric tenderness occurred in almost one-half of the cases and was regarded as of confirmatory value. Both groups of cases showed a tendency to high gastric acidity, more marked in the duodenal, but it is emphasized that such high acidity may occur in individuals free of all evidence of disease and so in itself cannot be accepted as evidence of ulcer.

The roentgenologic findings may be summarized as follows:

1. The roentgenologic diagnosis was correct in 94 per cent of the gastric and 88 per cent of the duodenal ulcers.
2. The most important roentgenologic diagnostic sign was the filling defect.
3. In 23 cases, that were diagnosed either pyloric stenosis, gastroduodenal ulcer or pyloric obstruction only six ulcers seemed to be pyloric in origin, the others being distinctly duodenal.
4. Healed ulcers give similar filling defects to adhesions or ulcer, but do not have associated suggestive fluoroscopic phenomena.

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LATE RESULTS OF SURGICAL TREATMENT OF PEPTIC ULCER BASED ON A STUDY OF 678 CASES.

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I. Introduction. There are few internists or surgeons at the present day who advocate the treatment of peptic ulcer by any single therapeutic measure; it is generally admitted that certain types of ulcer are best treated by medical therapeutics, others by surgical measures. Much of the confusion that has existed in the past in regard to the results of treatment by these two radically different methods has been due partly to the fact that both internists

and surgeons have been prone to draw conclusions after observing the results of their treatment over too short a period of time, and partly to the fact that patients who have been unsuccessfully treated by medical measures tend to gravitate to the surgeon, while the internist sees an unduly high proportion of the failures of surgery. To remedy this undesirable situation the Gastrointestinal Clinic* was organized several years ago (1923) at the Massachusetts General Hospital. In this Clinic the peptic ulcer cases are seen by a physician and a surgeon, who, not separately but together, arrive at a conclusion as to each individual case.

In all branches of surgery, as is natural and proper after a period of rapid technical development, emphasis is now being placed upon the late results of treatment. This is particularly important in surgery of the stomach and duodenum; no fundamentally new technical procedure has been introduced in this field for a considerable number of years, and sufficient time has therefore elapsed to evaluate the later results. The importance of the time element in estimating the efficacy of any operation has been, perhaps, the most valuable point brought out by the careful studies on the late result of surgical treatment of cancer, and has been considered of such significance that the term "cure" is there applied only with a qualifying clause as to the length of time which has elapsed since operation. The time factor is of the greatest importance also in estimating the late results of the surgical treatment of peptic ulcer, and is given detailed consideration in a later section of this report. There are, however, other and more complicated factors which make the results of surgical treatment of ulcer peculiarly difficult to judge, and a brief consideration of some of these factors is offered before presenting our findings.

Peptic ulcer is a disease of unknown etiology, characterized by spontaneous remissions and exacerbations of symptoms. The remissions are probably for the most part associated with the partial healing described by Crohn,¹ Mann² and others in their work on the process of healing in peptic ulcers; but there are many factors in the causation of symptoms from peptic ulcer that are not understood: the mechanism of pain sensations associated with ulcer, for example, is still a controversial point. It may safely be said that symptoms or lack of symptoms are often unreliable indications as to the condition of the ulcer, yet at the present stage of our knowledge they are our simplest and most reliable guides. Another factor which makes difficult the judgment of the late results of surgical treatment of peptic ulcer is the fact that the pathologic picture presents such widely differing aspects, varying from an ulcer that merely penetrates the mucosa and submucosa to one penetrating all coats and some adjacent organ, and from slight or no deformity

* This Clinic was organized by Dr. C. M. Jones and one of the authors; Dr. Jones was on leave of absence at the time this study was undertaken.

of the stomach or duodenum to the extraordinary picture presented by the so-called "hour-glass" stomach. The problem is rendered still more complex by the great number of types of procedure that may be employed in any given situation. In attempting to classify the results of the different operations, therefore, the number of cases comparable both as to pathology and as to surgical procedure must in many instances be small.

A further complication is introduced by the fact that operative procedures profoundly alter the physiology of the stomach and upper gastrointestinal tract, from the point of view both of the chemistry of the secretions and of the motor function. This altered physiology may result either in the formation of new ulcers* or in functional disturbances which may prove serious.

In setting forth our data we have made no attempt to oversimplify the problem, feeling that a detailed presentation of our findings will be of more value to the careful student of the subject than didactic conclusions which we ourselves might draw from our data.

Method. Material. This paper is based upon a study of 678 cases of peptic ulcer surgically treated in the Massachusetts General Hospital. The group includes the cases reported in 1922 by Scudder,³ together with the cases of peptic ulcer operated upon from 1919 to 1923, inclusive. They fall into three main groups as follows:

Duodenal ulcers	393
Gastric ulcers	261
Gastric and duodenal ulcers	24
	<hr/>
	678

Six hundred and fifteen of these patients were believed to be alive when this study was started.

Collection of Data. A letter was sent to each patient giving a definite appointment at the Gastrointestinal Clinic. One hundred and fifty patients responded in person to this request; 165 to a subsequent letter. All the remaining patients residing within a 10-mile limit of Boston whose letters were not returned "unclaimed" were visited; information concerning 42 cases was obtained in this way. Thus every patient in the community who could be traced through the postoffice was communicated with, in an effort to avoid any selection of cases. In 115 instances data were obtained from the hospital records of visits subsequent to operation. By these

* One of the most striking facts brought out by a review of the literature on the experimental production of acute ulcer in the duodenum or stomach is the uniform success which has attended all experimenters, whatever their method of procedure. This is due, undoubtedly, to the fact that ulcers readily occur in this highly specialized tissue following slight alterations in the physiology; there may be many different reasons why certain of these lesions become chronic.

various means we were able to collect information as to late results in 472 cases.

Classification of Results. Table I shows the main grouping of 393 duodenal ulcer cases and 261 gastric ulcer cases. We were unable to trace as long as two years after operation 68 of the duodenal cases, 66 of the gastric. Eighteen patients in the duodenal group and 15 in the gastric died one or more years after leaving the hospital and nothing, with one or two exceptions, is known of them beyond the mere fact of their death. In 30 cases in the duodenal group and 23 in the gastric group death followed operation. Two hundred and eighty duodenal ulcer cases and 159 gastric are analyzed for later results. Nineteen duodenal cases and 8 gastric had their first operation in another hospital; these are considered in the multiple operation group.

TABLE I.—ANALYSIS OF MATERIAL.

	Duodenal ulcer.	Gastric ulcer.
Cases not traced	68	66
Died one or more years after leaving hospital	18	15
Immediate mortality	30	23
Cases analyzed for later results	280	159
	<hr/>	<hr/>
	396	263
Less number included under two headings	3	2
	<hr/>	<hr/>
Total	393	261

In attempting to estimate the results of operation we have avoided the use of the words "cure" and "failure." Without precise knowledge, which is unattainable, as to the condition of the ulcer, the use of the word "cure" is obviously inaccurate; it is perhaps not too far-fetched to say that it is as little applicable here as in a consideration of the results of treatment of pulmonary tuberculosis. In regard to the term "failure;" this can hardly be used in the case of the many patients who have a return of ulcer symptoms of differing degrees of severity after having experienced a number of years of comfort and well-being as a result of operation; the operation may even have been a life-saving procedure at the time it was carried out, and it is manifestly unjust to consider such an operation a "failure," even though the good effects may not be permanent. We have, therefore, contented ourselves with dividing the patients into "A," "B" and "C" groups, as described below, on the basis of symptoms shown during the period of postoperative observation.

Group A includes patients who showed no return of ulcer symptoms throughout the period of observation; their diet was wholly or approximately unrestricted. Patients of Group B either showed a recurrence of mild symptoms, referable to ulcer but easily controlled by slightly restricted diet, or experienced at least one period of short duration, during which the symptoms were of moderate

severity but were amenable to simple treatment. The patients were not incapacitated or restricted in their work, and the operation had undoubtedly been of great value to them. Patients of Group C experienced at some time following operation a recurrence so severe as to hinder them greatly in their work, to incapacitate them, or require further hospitalization.

Of the total number of cases of duodenal ulcer (261) followed for from two to ten years or more after operation, 172 (66 per cent) were classified as "A" throughout their period of observation, 40 (15 per cent) were classified as "B" and 49 (19 per cent) as "C." The corresponding figures for the 151 gastric cases were: "A," 104 (69 per cent); "B," 19 (12.5 per cent); "C," 28 (18.5 per cent). On the basis of these figures, it might be said that operation gave satisfactory results throughout the period of observation in about 81 per cent of the cases of gastric and of duodenal ulcer. This method of grouping, however, does not give sufficient importance to the time element: The cases followed for a shorter period of time show fewer recurrences than those observed over a more extended period, and an average is therefore misleading.

The problem thus arose as to a satisfactory method of classifying the patients who were symptom-free for a number of years and then showed a recurrence of ulcer symptoms. These were listed as "A" during the period of well-being and then listed as "B" or "C" during the remainder of the time followed. If the patient developed symptoms so severe as to demand a second operation he was accounted "C" during the total time the case was followed after the development of symptoms. For example, suppose for two years after operation a patient was symptom-free, then developed such a severe recurrence of symptoms as to require a second operation. Such a patient would appear as an "A" in the group observed two years after operation; he would then be counted as "C" throughout the remainder of his period of observation, for presumably without the second operation he would have continued to have trouble. The results of second operations are discussed later under the heading of "multiple operations."

Results. In Table II a detailed report of the cases followed from two to ten years is presented. The classification of the total group of duodenal ulcers (261) is given two years after operation; 232* of these cases are reported on four years after operation, 165 six years after, 105 eight years after and 64 ten or more years after. The corresponding group figures for the gastric cases are: 151 two years after operation, 136 four years after, 109 six years after, 77 eight years after and 51 ten or more years after. To the right of the column of figures showing the number of "B" and "C" patients is a statement as to the time the recurrence of symptoms took place.

* Twenty-nine of the 261 cases either had been operated on less than four years before this study was made or could not be traced after the two-year period.

TABLE II.—CLASSIFICATION OF CASES.

Duodenal ulcer.		Gastric ulcer.	
Two Years After Operation.			
Group A . . .	197	117	
Group B . . .	36 (31 showed recurrences within first year; 5 were "A" for 1 year)	16 (15 showed recurrences within first year; 1 was "A" for 1 year)	
Group C . . .	28 (22 showed recurrences within first year; 6 were "A" for 1 year)	18 (16 showed recurrences within first year; 2 were "A" for 1 year)	
	<hr/> 261	<hr/> 151	
Four Years After Operation.			
Group A . . .	171	105	
Group B . . .	28 (25 showed recurrences within first year; 3 were "A" for 1 year)	13 (12 showed recurrences within first year; 1 was "A" for 1 year)	
Group C . . .	33 (21 showed recurrences within first year; 5 were "A" for 1 year; 7 were "A" for 2 years)	18 (14 showed recurrences within first year; 2 were "A" for 1 year; 2 were "A" for 2 years)	
	<hr/> 232	<hr/> 136	
Six Years After Operation.*			
Group A . . .	114	76	
Group B . . .	20 (15 showed recurrences within first year; 1 was "A" for 1 year; 4 were "A" for 4 years)	12 (9 showed recurrences within first year; 1 was "A" for 1 year; 2 were "A" for 4 years)	
Group C . . .	31 (15 showed recurrences within first year; 4 were "A" for 1 year; 7 were "A" for 2 years; 5 were "A" for 4 years)	21 (10 showed recurrences within first year; 1 was "A" for 1 year; 3 were "A" for 2 years; 7 were "A" for 4 years)	
	<hr/> 165	<hr/> 109	
Eight Years After Operation.			
Group A . . .	80	51	
Group B . . .	9 (8 showed recurrences within first year; 1 was "A" for 3 years)	11 (7 showed recurrences within first year; 1 was "A" for 1 year; 2 were "A" for 4 years; 1 was "A" for 6 years)	
Group C . . .	16 (6 showed recurrences within first year; 1 was "A" for 1 year; 4 were "A" for 2 years; 1 was "A" for 4 years; 4 were "A" for 6 years)	15 (6 showed recurrences within first year; 1 was "A" for 1 year; 3 were "A" for 2 years; 4 were "A" for 4 years; 1 was "A" for 6 years)	
	<hr/> 105	<hr/> 77	
Ten Years After Operation.			
Group A . . .	53	36	
Group B . . .	2 (Both showed recurrences within first year)	6 (5 showed recurrences within first year; 1 was "A" for 4 years)	
Group C . . .	9 (2 showed recurrences within first year; 1 was "A" for 1 year; 2 were "A" for 2 years; 2 were "A" for 6 years; 2 were "A" for 8 years)	9 (4 showed recurrences within first year; 3 were "A" for 2 years; 2 were "A" for 4 years)	
	<hr/> 64	<hr/> 51	
(30 of these 64 cases were followed for more than 10 years, 3 of them developing severe symptoms)		(19 of these 51 cases were followed for more than 10 years; none of them developed symptoms)	
Group A, symptom-free.		Group B, mild symptoms.	
		Group C, severe symptoms.	

* The figures of the

* The figures of the six-year group are shown in percentage form in Fig. 1.

It will be noted that about 11 per cent developed severe recurrences at the end of two years. In the cases followed four years the percentage of severe recurrences was about 14; in those followed six years, 19. After six years the percentages fall off somewhat, being 15 and 14 per cent for the cases followed eight or ten years; this is probably due to the fact that during this later period proportionately fewer of the cases developing severe symptoms could be traced. In the gastric cases the percentage of recurrences in the two-year, four-year and six-year groups was about the same as that for the duodenal ulcer cases. In the eight-year or ten-year groups it was somewhat higher, being about 19.5 and 17.6 per cent respectively.

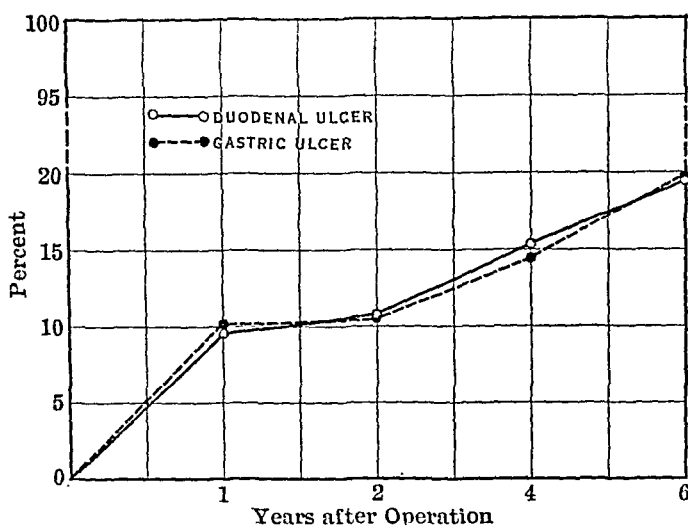


Chart I shows in percentage form the recurrences of severe symptoms that took place in the group followed for six years, and the time at which these occurred. See also Table II, cases followed six years.

In order to present in more detail the proportion of recurrences and the length of time after operation at which these occurred, the findings in regard to all the patients we were able to observe six years or more after operation which were given in Table II are also shown in percentage form in Chart I. This six-year group was selected because it consisted of a fairly large number of cases considered after a sufficient length of time had elapsed since operation to make a study of the results especially valuable. It will be noted in Chart I that while the greatest percentage of relapses occurred within the first year, there were many recurrences throughout the whole period of observation, so that at the end of six years about 19 per cent of both gastric and duodenal ulcer patients had developed severe symptoms, as against 11 per cent that showed recurrences at the end of the second year. In cases showing mild recurrences the symptoms appeared chiefly within the first year (Table II), the increase during the remainder of the six years being small,

Operative Procedures, Duodenal. In Table III the cases of duodenal ulcer are arranged according to the operation performed, the last three columns showing the groups in which these cases were finally placed on the basis of later symptoms. We see here that posterior gastroenterostomy formed the essential part of the operation in 230 cases, and was thus, either alone or in combination with other procedures, the major operative attack on duodenal ulcer. Of these 230 cases, 152 remained completely free from symptoms throughout the period of observation, and are placed in Group A; 37 showed mild recurrences at some time following operation. Definitely severe symptoms recurred in 41 cases; these cases were placed in Group C.

TABLE III.—OPERATIVE PROCEDURES, DUODENAL ULCER.

Operative procedure.	Total number.	Group A.	Group B.	Group C.
Posterior gastroenterostomy alone	147	92	28	27
Posterior gastroenterostomy + infolding	70	52	6	12
Posterior gastroenterostomy + excision	10	6	2	2
Posterior gastroenterostomy + pylorus ligature	3	2	1	..
Pylorectomy plus posterior gastroenterostomy	10	10
Excision or infolding of ulcer	16	6	3	7
Pyloroplasty	1	1
Pyloroplasty plus excision	4	3	..	1
Total	261	172	40	49

The 10 cases where pylorectomy was performed, with continuity of the intestine reestablished by posterior gastroenterostomy, all appear in Group A. This operation was carried out for chronic ulcers situated near the pylorus and usually causing considerable organic obstruction of the pylorus. In 16 instances ulcers were excised or infolded without gastroenterostomy; of these, 14 were cases of acute perforation and will be discussed under that heading in a later section. Some type of pyloroplasty was carried out in 5 cases with good results in 4 instances.

Operative Procedures, Gastric. Table IV is similar in purpose to Table III and shows the operative procedures employed for gastric ulcers. It is interesting to note that of the small group of cases where posterior gastroenterostomy alone was performed, only 1 case showed return of severe symptoms. Posterior gastroenterostomy combined with infolding or excision of the ulcer was carried out in 72 cases, satisfactory results being obtained in 64 instances.

In 26 cases the ulcer was treated by infolding or excision alone, severe ulcer symptoms recurring in 12 instances or almost half the total number. These latter cases belong to the early period of development of knowledge concerning the surgical treatment of gastric ulcer, and serve to emphasize the soundness of the opinion

now current that excision of a gastric ulcer is unsuccessful in a large proportion of cases unless combined with a posterior gastroenterostomy.

TABLE IV.—OPERATIVE PROCEDURES, GASTRIC ULCER.

Operative procedure.	Total number.	Group A.	Group B.	Group C.
Posterior gastroenterostomy alone	24	20	3	1
Posterior gastroenterostomy + infolding	29	22	5	2
Posterior gastroenterostomy + excision	43	35	2	6
Excision alone	23	8	4	11
Infolding alone	3	2	..	1
Partial gastrectomy	17	12	2	3
Pylorotomy	4	3	..	1
Sleeve resection	4	1	2	1
Pyloroplasty	3	1	..	2
Gastrogastrostomy	1	..	1	..
Total cases	151	104	19	28

Partial gastrectomy or pylorotomy was carried out in 21 instances, with recurrence of severe symptoms in 4 cases.

Other operative procedures are listed, but their number is too small to furnish data of any importance.

Gastric and Duodenal Ulcer Present in the Same Patient. The operations performed on the 24* patients in whom there was an active lesion of both stomach and duodenum, were as follows: partial gastrectomy on 7, cuff resection on 1, posterior gastroenterostomy combined with excision or infolding of the ulcer on 13, anterior gastroenterostomy on 1, pyloroplasty on 1 and gastroenterostomy with gastroduodenostomy on 1. Three of these 24 patients died following operation; 8 we could not trace; 6 were observed for six years or more, 5 for three years or more and 2 for two years; of the 13 we were able to trace, 1 showed mild recurrence of symptoms and 12 remained symptom-free.

The late results of operation on this small group are strikingly good, perhaps because there was a large number of the more radical type of operation. The good results, however, are somewhat counterbalanced by the 3 deaths following operation. In 2 of these latter cases there was an hour-glass constriction of the stomach in addition to the duodenal ulcer; in the third case the inflammatory reaction around stomach and duodenum was so extensive that only an anterior gastroenterostomy could be carried out; this case developed a fatal obstruction during convalescence.

Operative Mortality. The factors governing the mortality rate following operation for peptic ulcer are complex. The outstanding circumstances that influence it are as follows: the age and general condition of the patient, the seriousness of the local pathology, the type of operation selected.

* In 8 other cases during operation for gastric ulcer the scar of a healed duodenal ulcer was found.

The causes of death following operations for duodenal and gastric ulcers are listed in Table V. There were 30 deaths in the duodenal series and 26 in the gastric. There were 4 deaths following operation for gastrojejunal ulcer, and these are included in Table V: 2 listed in the duodenal series and 2 in the gastric, according to the site of the primary ulcer. Six of the deaths followed operations for acute perforation: 5 duodenal and 1 gastric. The mortality, excluding these cases of acute perforation, was 6 per cent for the duodenal cases and 9 per cent for the gastric. The average age of these patients was a little over fifty years: 10 in the duodenal series and 8 in the gastric series were over sixty years of age.

TABLE V.—IMMEDIATE MORTALITY.

Causes of death.*	Duodenal ulcer cases.	Gastric ulcer cases.
Peritonitis	14	5
Pulmonary complication:		
(a) Pneumonia	4	8
(b) Pulmonary embolus	4	2
(c) Lung abscess	1	
(d) Gangrene of lung	1	
	—10	—10
Shock	2	3
Hemorrhage	2	3
Cardiac embolus	1	
Uremia	1	
Persistent vomiting	3
Fatty degeneration of liver	1
Septic parotitis	1
	— 6	—11
	<hr/> 30	<hr/> 26

* Four deaths following operation for gastrojejunal ulcer are included in this table: 2 listed in the duodenal series, 2 in the gastric, according to the site of the primary ulcer. Six of the deaths followed operations for acute perforations: 5 duodenal, 1 gastric.

The 6 cases of pulmonary emboli following operations for duodenal or gastric ulcers is a rather surprisingly large number when one recalls that the venous drainage from the operative field is into the portal system where emboli would be filtered out by the capillaries of the liver.

Among the fatal duodenal cases the ulcer was described as "penetrating" in 10 instances; the 2 deaths from hemorrhage belong in this group, the bleeding occurring from a deeply penetrating ulcer that could not be excised. One patient showed cirrhosis of the liver in addition to the ulcer. Among the fatal gastric cases a chronic perforation of the ulcer into the substance of the liver or pancreas was found in 4 instances. There was 1 hour-glass deformity. In 3 cases ulcers of both stomach and duodenum were present.

II. Acute Perforations. Of the total group of peptic ulcer cases, 39 had a history of acute perforations: 15 of the gastric ulcers and

24 of the duodenal ulcers. Of these, 7 had their first operation at another hospital and entered the Massachusetts General Hospital because of recurrence of symptoms; they are considered in the "multiple operations" group of cases. Of the 39, only 3 were females, 2 gastric and 1 duodenal.

In 3 of the 15 gastric cases the perforation occurred without any previous ulcer symptoms; in 1 case, after a few days of gastric distress. These 4 perforations were in patients under twenty-seven years of age. The average age of the remaining patients with perforated gastric ulcer was 43.6. The average duration of symptoms before perforation was 8.5 years.

Of the 24 duodenal perforations, 6 had only a few days of ulcer symptoms before the perforation occurred. Three of these cases were under twenty-seven years of age and 3 were thirty-six years or over; the age of the remaining cases in which the duration of symptoms before operation is recorded averaged 35.2 years. The average duration of symptoms was 7.4 years.

Contrasting the gastric and duodenal cases of perforation, it will be noted that in both there is a small group where perforation occurred either with no previous symptoms or after a very short prodromal stage. In the gastric group all such cases were in young persons; in the duodenal group half these cases were under thirty years and half were middle-aged or old.

Results of Operation for Acute Perforations. Thirty-two patients were operated on at the Massachusetts General Hospital at the time of an acute perforation, 6 of whom died following operation, giving an immediate mortality of 18.7 per cent. The cause of death in 5 of these cases was general peritonitis and in 1, hemorrhage.

Later results are known in 24 cases as follows: 7 of these cases had had infolding of the ulcer and posterior gastroenterostomy; of these, 6 had no recurrence during the five years they were observed; 1 had a recurrence of severe symptoms (perforation of a gastrojejunal ulcer) after seven years of well-being. In 17 cases an infolding of the perforation alone was carried out; of these, 11 had recurrence of severe symptoms, for the most part within the first year after operation; 3 had recurrence of mild symptoms; 3 had no recurrence during the six years they were under observation.

It is clear from the above figures that the prognosis in those cases where it is possible to perform a posterior gastroenterostomy as well as to close the ulcer is much better than in cases where only closure of the perforation can be carried out. It should be emphasized, however, that closure of an acute perforation is a life-saving procedure, and if a further operation is likely to add to the risk it should not be attempted. It is only in a small group of cases where the patient is in good general condition and is operated upon within a few hours of the perforation that anything more radical than a simple closure should be attempted.

Multiple Operations. Forty-nine cases were operated upon more than once; 4 of these were operated upon three or more times. In 22 instances the first operation was performed at the Massachusetts General Hospital; in 27 cases it took place at another hospital. Of the group of cases not given relief by operation, those that come to a second operation are of great interest because they afford an opportunity to determine accurately, in most instances, the exact nature of the pathology responsible for the persistent or recurrent symptoms.

Pathology Found at First Operation. Of the 49 cases coming to a second operation, 32 are believed to have shown duodenal ulcer at their first operation and 17 gastric. Of the 32 patients with duodenal ulcers, there were 10 whose first operation was for acute perforation; 2 patients with gastric ulcers had been operated upon for acute perforation; for more detailed discussion of these cases, see section on acute perforations. Of the remaining cases, there were 2 in which more than one ulcer was found in the duodenum at the time of the first operation; 2 in which more than 1 gastric ulcer had existed. It is interesting to note that in 5 instances the duodenal ulcer found at the first operation was described as "small." Among the gastric cases there was 1 in which the stomach showed an hour-glass deformity. There was nothing outstanding in the pathology described for the remaining cases.

Symptomatic Relief following First Operation. The average period of symptomatic relief following the first operation was about one and a half years for the duodenal group and about half as long for the gastric. Four patients in the duodenal group remained symptom-free for six years or over, and then developed severe symptoms. A gastrojejunal ulcer was found at the second operation in 3 of these cases. The fourth case was of special interest: the first operation had disclosed multiple ulcers of the duodenum, and a posterior gastroenterostomy was performed; the patient was without symptoms for ten years and then developed severe symptoms requiring the second operation, which revealed the fact that the duodenal ulcers had healed and that the later symptoms were due to a large ulcer of the lesser curvature of the stomach.

The average time period between the first and second operation was about four years for both groups; there were 9 instances in which the interval was seven years or more.

In the great majority of cases (43) the chief symptom that brought the patient to a second operation was pain. In 5 instances the presenting symptom was hemorrhage and in 1 instance, vomiting.

The Second Operation. Of the 49 cases requiring further surgical treatment, a gastrojejunal ulcer was found at the second operation in 14 instances. In 9 instances the posterior gastroenterostomy had been carried out for duodenal ulcer and in 5 instances for gastric. In 6 cases with gastrojejunal ulcer the gastroenterostomy had been performed at the Massachusetts General Hospital. Since there

were 357 posterior gastroenterostomies performed in this series in which late results were noted, the instances of proven gastrojejunal ulcer form 1.7 per cent. For the most part the procedure employed at the second operation consisted in resection of the ulcer and stoma; in some instances a new posterior gastroenterostomy was performed. There was 1 case in which an exploratory operation only was carried out, the general condition of the patient not permitting a radical operation; in another patient the only procedure carried out was the closure of a perforation. Among the 14 cases of gastrojejunal ulcer there were 4 deaths. The late results of operation on the other 10 cases were in the great majority of instances decidedly poor. For more comprehensive and detailed accounts of certain of these patients, a recent article by Davis⁴ should be consulted.

Of the remaining 35 cases requiring a second operation, the first operation had been for duodenal ulcer in 23 instances and for gastric ulcer in 12.

In 10 of the 23 duodenal ulcer cases posterior gastroenterostomy did not constitute part of the first operation; the recurrent symptoms in all of this group were due to a chronic duodenal ulcer. In 6 of these 10 cases (4 of which were followed six years or longer) a posterior gastroenterostomy at second operation gave good results; in 1 instance the patient died following the operation; in 2 the late results are unknown; in 1 the late results were poor.

In 13 of the 23 cases where the first operation was for duodenal ulcer a posterior gastroenterostomy had constituted the major part of the original procedure. In 8 of the 13 some abnormality other than gastrojejunal ulcer was described as having developed in connection with the posterior gastroenterostomy: "stenosis," "adhesions," "poorly placed," etc.; in 6 of these 8 a chronic ulcer of the duodenum also existed; in 2 the ulcer had apparently healed, the symptoms presumably being due to the malfunction of the enterostomy. In 5 of the 13 cases the gastroenterostomy performed at first operation was satisfactory, the later symptoms being due in most instances to chronic duodenal ulcer usually complicated by "dense adhesions;" 1 case showed that the duodenal ulcer had healed and a gastric ulcer had formed.

The procedures at second operation on the above group of 13 were varied and the results in most cases disappointing. There were 2 pylorectomies, 1 giving good results for six years, the other giving moderately good results. There was 1 gastric resection, result unknown; 2 pyloroplasties, result unknown; lysis of adhesions in 2 cases, followed by recurrence of symptoms. The posterior gastroenterostomy was disconnected in 5 instances, with poor results twice, with moderate success once, and with result unknown twice. One excision of a gastric ulcer gave good results for five years.

In 9 of the 12 cases in which the original operation was for gastric

ulcer no posterior gastroenterostomy had been carried out at the first operation: the activity of the old ulcer was responsible for the recurrence of symptoms in 3 of these; obstruction at the pylorus from the old ulcer in 2; a new gastric ulcer had formed in 3 cases, the original ulcer having been excised; in 1 instance a duodenal ulcer had formed. Eight of these cases were treated by posterior gastroenterostomy; 1 by partial gastrectomy. The immediate results were good in all instances; 2 of the cases which were treated by posterior gastroenterostomy showed a recurrence of symptoms after one and two years, respectively; the others, 3 of which have been followed four years or more, have shown no recurrence.

In 3 of the 12 cases in which the first operation was for gastric ulcer, a posterior gastroenterostomy formed a part of the procedure. In 2 of these 3 a chronic gastric ulcer was responsible for the recurrence of symptoms. One of these was complicated by an hour-glass deformity: an anterior gastroenterostomy was performed, but the patient did not survive the operation. In the second case it was not possible to carry out any radical procedure: a drain was placed to the region of an inflammatory mass on the lesser curvature; the patient improved after the operation but died two years later. The third case showed a twist of the jejunum near the gastrostomy opening: the posterior gastroenterostomy was disconnected and a Roux operation carried out; the patient was symptom-free during the two years he was followed.

III. Factors Affecting Prognosis and Choice of Operation. In order to see if any guide could be obtained for the selection of cases suitable for operation, or any prediction be made as to the outcome of operation, an attempt was made to correlate the late results of the operation with the preoperative and operative findings.

The patients were divided as before into "A," "B" and "C" groups. The following points were then tabulated for the several groups: the ratio of male to female; the average age of patients; the duration of symptoms before operation; the presence or absence of six-hour residue as shown by Roentgen ray examination; the average total acidity; the location and size of the ulcer. The appendectomies performed in connection with operations for duodenal ulcer were also tabulated. The results are set forth in Table VI.

The Ratio of Male to Female Patients. Duodenal ulcer, it is generally agreed, occurs about four times as often in males as in females. This ratio was found to hold true in all three groups of patients ("A," "B" and "C"). This is an interesting fact, for the differences in mode of life and occupation of men and women might be expected to exert some influence on the recurrence of symptoms. In the gastric cases a striking difference between the sexes is shown in regard to the recurrence of symptoms, for while the ratio of sex in patients that remained symptom-free or developed

only mild symptoms is 1 to 1, four times as many males as females developed severe recurrence of symptoms. The reason for this is not clear.

Average Age of Patients and Duration of Symptoms Before Operation. It will be noted that in the duodenal ulcer cases the patients who remained symptom-free following operation averaged two and a half years older at time of operation than those who developed mild symptoms, and seven years older than those who developed severe symptoms. It will also be noted in the duodenal cases that the duration of symptoms before operation was longer in the cases that had no recurrence of symptoms than in the other two groups.

These findings in regard to the age of the patients and the duration of preoperative symptoms confirm the current opinion that it is desirable to treat cases of duodenal ulcer by medical therapeutics as long as possible, not only because a certain number of cases will be cured by that means, but also because the results of operation will be definitely better in a chronic ulcer of long standing.

The patients with gastric ulcer when thus analyzed show a marked contrast to the patients with duodenal ulcer. The average age of the gastric patients at the time of operation was practically the same in the "A," "B" and "C" groups. The duration of symptoms before operation was shorter in the cases that had no recurrence of symptoms than in the other two groups. These figures indicate that postponing operation did not result in a more favorable outcome.

Six-hour Residue. In the duodenal ulcer cases, considerable six-hour retention of bismuth was noted in 72 instances; it was absent or slight in 161 examinations. As shown in Table VI, 58 of the 72 cases appear in Group A, 6 in Group B and 8 in Group C. It is interesting to find such a large proportion listed in the group showing no recurrence of symptoms. It has been noted for a long time in the literature that patients showing obstruction from duodenal ulcer formed a particularly favorable group for surgical treatment, thus leading Eiselsberg⁵ and others to advocate deliberate closure of the pylorus, by fascial tie or other procedure, in addition to a posterior gastroenterostomy. The results of this procedure have been adversely criticized by many writers. The suggestion is here made that the reason so many cases that showed stasis in our series obtained good results from operation was due not to the obstruction of the pylorus *per se*, but to the fact that the lesions causing marked obstruction are chronic, indurated lesions, the type which yields best to surgical treatment.

Gastric stasis in the presence of gastric ulcer was noted in 67 instances. As shown in Table VI, it was found 48 times in cases placed in Group A, 7 times in those of Group B, 12 times in those of Group C, which consisted all-told of only 28 cases. Thus, while it was often present in cases remaining symptom-free, it was also

found in a high proportion of the cases later developing severe symptoms.

TABLE VI.

	Duodenal ulcer.			Gastric ulcer.		
	Group A.	Group B.	Group C.	Group A.	Group B.	Group C.
Ratio of males to females	4 to 1	4 to 1	4 to 1	1 to 1	1 to 1	4 to 1
Average age in years	42	39.5	35	45.5	46	46
Average duration of symptoms before operation, in years	7.7	6.5	4.8	6.7	12	8
Six-hour residue	58	6	8	48	7	12
Average total acidity, cc. N/10 solution	63.7	48	58.7	54	52	56
Location of ulcer:						
Anterior surface	4	0	1
Posterior surface	10	1	3
Lesser curvature	72	8	24
Near the pylorus	21	3	3
First portion	135	34	29
Second portion	8	1	1
Size of ulcer:						
Large	34	8	5
Small	18	8	11
Appendectomies performed on duodenal ulcer cases, per cent	20	11	25

The Average Total Acidity. The average total acidity was within normal limits in both duodenal and gastric ulcer cases and showed little variation in the "A," "B" and "C" groups. In view of the stress that has been laid on the rôle of acid in causing recurrence of ulcer symptoms after operations, it is striking that in the patients with duodenal ulcer who later had recurrence of symptoms, the total acidity before operation averaged slightly lower than it did in the patients who remained symptom-free. It is interesting, however, that of the 6 cases (4 duodenal and 2 gastric ulcers) later developing gastrojejunal ulcers, the total acidity before the first operation was recorded in 5 instances, and in each case a definitely high value was found.

Location of the Ulcer. In the great majority of cases the duodenal ulcer was described as located in the first portion of the duodenum. This is true for all three groups. About two-thirds of the gastric ulcers were described as occurring on the lesser curvature. The next largest number was described as occurring in the region of the pylorus. No important relation is brought out by our figures between the location of the ulcer and the results of operation.

Size of the Ulcer. It is interesting to note (Table VI) that in the group of patients with duodenal ulcer who developed severe symptoms after operation (Group C) the ulcer was described as "small" almost twice as many times as "large," while in the group that remained symptom-free (Group A) the reverse was true.

This brings out again the point that the large, callous, duodenal ulcer is the more favorable type for operation.

Effect of Appendectomy. Since Balfour⁶ has stressed the importance of infections of the appendix as an etiologic factor in the recurrence of ulcer symptoms, it is interesting to note (Table VI) that removal of the appendix did not in this series seem to lessen the recurrence of ulcer symptoms, the groups showing such recurrences having had a higher percentage of appendectomies (36 per cent) than the group showing no recurrences (20 per cent).

Summary. This study is based upon 678 cases, grouped as follows: 393 duodenal ulcers and 261 gastric ulcers; 24 gastric and duodenal ulcers in the same patient. In 472 of these cases information was obtained as to the condition two or more years after operation.

About 11 per cent of the duodenal ulcer patients showed a severe recurrence of symptoms by the end of two years, 14 at four years, 19 at six years, 15 at eight years and 14 at ten years. The figures for the gastric cases were about the same, except that the percentage of recurrences in the eight- to ten-year groups was somewhat higher—19.5 and 17.6 respectively. The results in the cases of gastric and duodenal ulcer in the same patient are given in detail in the text; in general they were good.

Excluding the cases of acute perforation, the operative mortality was 6 per cent for the duodenal ulcer cases and 9 per cent for the gastric. The average age of the patients dying after operation for duodenal ulcer was fifty-one, 10 being over sixty years of age; of the gastric patients, fifty, 8 being over sixty years of age.

Section II deals with acute perforations and multiple operations. Twenty-four of the duodenal patients and 15 of the gastric patients had a history of acute perforation. The average duration of symptoms before the perforation was about eight years; but there were a few cases where the perforation occurred with brief, if any, previous symptoms. In the gastric group all such cases occurred in young persons; whereas in the duodenal group half were in middle-aged or elderly persons. The immediate mortality was 18.7 per cent. The late results show that the prognosis in the small group where it is possible to perform a gastroenterostomy as well as to close the perforation, is much better than in cases where closure alone is possible. It is emphasized, however, that closure of an acute perforation is a life-saving procedure, and if further operation is likely to add to the risk it should not be attempted.

Of the 49 cases having more than one operation, 32 are believed to have shown duodenal ulcers at their first operation and 17 gastric. The duration of symptomatic relief following the first operation averaged about one and a half years for the duodenal group and a little less for the gastric. The average time period between the first and second operations was about four years. In the great majority of cases (43) the chief symptom that brought the patient

to a second operation was pain; in 5 cases the presenting symptom was hemorrhage; in 1 instance, vomiting.

Among the cases twice operated upon, a gastrojejunal ulcer was found in 14 instances; in 6 of these the gastroenterostomy had been performed at the Massachusetts General Hospital and shows 1.7 per cent of proven gastrojejunal ulcers among the cases from this hospital. The results of the operation for gastrojejunal ulcers were in the great majority of cases poor.

Of the remaining 35 cases requiring a second operation, approximately half had no gastroenterostomy at their first operation. A gastroenterostomy at the second operation gave in general excellent results. In the group where a gastroenterostomy constituted part of the first operation the results of the second operation were usually disappointing (see text).

Section III describes an attempt to correlate the preoperative and operative findings with the late results. The following points were brought out:

A greater proportion of the men than of the women with gastric ulcer developed severe recurrence of symptoms; this did not hold true for duodenal ulcer patients (Table VI). The younger patients with duodenal ulcer showed a higher incidence of recurrence than did the older group. The average duration of symptoms before operation in duodenal cases was almost twice as long in the patients who remained symptom-free as among those who showed severe recurrences, indicating clearly that an ulcer of long standing responded more favorable to operation. In the gastric cases no inference as to late results could be drawn from the age of the patient or the duration of symptoms before operation.

The results of operation in the duodenal ulcer group were better in those cases that showed evidence of gastric stasis prior to operation. The suggestion is made that this is not due to obstruction of the pylorus *per se*, but to the fact that marked obstruction is caused by chronic, indurated lesions—the most favorable type for operation. No relation could be found between the total acidity prior to operation and the later development of symptoms, except that the patients who later developed gastrojejunal ulcer showed a high acidity prior to the first operation. The small ulcer of the duodenum showed a greater recurrence of symptoms than the larger, calloused ulcer.

Removal of the appendix in connection with the operation for duodenal ulcer did not, in this series of cases, appear to lessen the recurrence of ulcer symptoms.

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A COMPARISON OF THE LATE RESULTS OF AMBULATORY AND HOSPITAL TREATMENT OF PEPTIC ULCER.*

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AND

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IN 1926 we reported¹ a statistical and diagnostic study of 250 patients suffering from peptic ulcer (gastric 44 cases, duodenal 206 cases). We noted particularly then that our clinical diagnostic errors, apparently proved by operation on 90 patients, were 4.5 per cent, and that we believe our diagnoses in the unoperated cases were as accurate as in those operated upon. We also noted that half of our patients suffering from duodenal ulcer dated the onset of their symptoms before the age of twenty-five years, while only one-fourth of gastric ulcer patients placed the onset of symptoms before the age of twenty-five years. The average duration of gastric ulcer symptoms before consulting us had been only half the duration of symptoms of those suffering from duodenal ulcer. A history of massive hemorrhages was obtained from 15 per cent of the patients suffering from duodenal ulcer, and from 30 per cent of the patients suffering from gastric ulcer. Acute perforation occurred in nearly 6 per cent of all patients.

From these 250 patients have now been selected those suitable for follow-up study of medical results; attempting to ascertain, by careful inquiry, the present condition of all patients who were advised regarding medical treatment. We have found few statistical studies in medical literature on the late results of hospital medical treatment and no figures whatever on the late results of ambulatory treatment of peptic ulcer.

What are the results of medical treatment for peptic ulcer? The literature is rich in estimates of from 60 per cent to 90 per cent of cures by medical means, but there are remarkably few articles from which accurate conclusions, ascertained by follow-up study after years, can be obtained. Most authors have stressed the importance of hospitalization for three or four weeks and very careful supervision up to a year or more after leaving the hospital.

The noteworthy work of Sippy has, strange to say, never had a follow-up study by himself or his coworkers. Other clinicians using Sippy's method, particularly Jones,² Phillips,³ White,⁴ and Shattuck,⁵ have not approached Sippy's claimed percentage of cures. Smithies⁶ has reported a series of 470 cases treated by his

* Read before the American Gastro-enterologic Association at Washington, D. C., April 30, 1928. From the Virginia Mason Hospital.

own method, in which he states there is a "cessation of the ulcer process" in 77 per cent.

As far as we can learn, there are no published results of ambulatory treatment, except that White⁴ states that his cases of duodenal ulcer have often been treated by ambulatory methods. Ambulatory treatment is recognized as good by Alvarez,⁷ Rehfuß,⁸ and others; but no results have been published.

It is strange that internists have not been more active in the follow-up study of patients suffering from peptic ulcer. Surgeons have set a good example in this field. Balfour⁹ has reported 1000 cases after gastroenterostomy for duodenal ulcer, and shows 88 per cent of good results after ten years; the 12 per cent remaining manifestly does not include his remote mortality from ulcer or other causes. Various other surgeons have published good results, and our own experience confirms the observation that gastroenterostomy, when successfully done, gives a high percentage of clinical cures. For this reason we have had far more than the average internist's leaning toward surgical treatment for ulcer.

MEDICAL TREATMENT. Our interest in peptic ulcer goes back some eighteen years. Training in a large surgical clinic, where peptic ulcer was usually treated surgically, made us feel that such treatment was usually the procedure of choice. On entering private practice in 1917, we began to find that patients who refused operation often did well on ambulatory treatment of the casual kind. We put a number on bismuth and magnesia tablets or other alkalis, frequent feeding, and reasonable care of diet. Such patients did well as a rule; but occasional failures and Sippy's brilliant writings caused us to put some 30 selected patients under hospital management between 1920 and 1923.

Patients advised hospital treatment were a selected group. They were selected for such treatment because they were intelligent, younger than the average, anxious to coöperate, and without surgical complications. This selection gave as an average patient a male, aged thirty-one years, with a history of periodic trouble for seven years. Such patients were treated as accurately as possible, both in the hospital and afterward.

Hospital treatment almost always brought immediate relief; but as time elapsed we found that many patients had a return of trouble, in spite of every care and advice that we could give them regarding diet and medication. We were forced to the opinion that it was doubtful whether these favorable cases (with three or four weeks of training in the hospital behind them and a year or more of extreme care afterward) did better than those on casual ambulatory treatment.

This impression became so definite that since 1923 we have practically given up hospital medical treatment. Since that date we have treated medically in the hospital only patients too ill to be on their feet.

Those patients, therefore, who were advised ambulatory treatment more than five years ago were usually in one of two groups: either unable to take medical treatment in the hospital, or they requested ambulatory treatment for temporary relief with the idea of later coming to operation. Several of the latter group, whom we felt rather urgently surgical, had so much relief that they now consider themselves free from trouble. In the past five years we have usually advised ambulatory treatment in cases of uncomplicated duodenal ulcer and in a very few cases of gastric ulcer.

The treatment advised has been simple and has emphasized frequent feedings. We have advised a relatively smooth diet, avoiding highly seasoned foods, fried foods, and notably indigestible foods. We have cautioned against overloading the stomach and against irregular hours. We have advised about the hygienic care of the bowels. We have usually advised bismuth and magnesia tablets or other alkalis an hour after meals; though patients have often discontinued such medication of their own accord, to resume medication later if there were any suggestion of trouble. Each patient has been given a talk on the importance of proper living, on the avoidance of mental stress and worry, and on the evils of tobacco and alcohol for the ulcer patient. We have laid most emphasis, however, on frequent feedings; and this is usually reported by the patient to be the most valuable feature of the treatment, rather than the kind of food or drug. We have done our best to avoid making invalids or neurasthenics of our patients. They have had no period of bed or hospital treatment, and they have continued in their usual occupation.

Such measures have given so much relief that the majority of patients have considered themselves entirely relieved.

Results of Medical Treatment. We have interviewed or obtained written reports from two-thirds of all patients upon whom we have not actually operated. We then excluded from this study those who left us to seek operation elsewhere, or those who were diagnosed as having complicating diseases requiring operation, particularly gall-bladder disease or appendicitis.

Approximately 100 patients were left available for study, who had had a diagnosis made of peptic ulcer two to ten years ago, and had been given instructions regarding medical treatment.

We carefully reviewed these 100 case histories with their Roentgen ray and laboratory findings, and excluded each case in whom there was any doubt regarding the clinical diagnosis. This left 86 patients (6 gastric ulcer, 80 duodenal ulcer) in whom we feel sure of the diagnosis (allowing 5 per cent or less for clinical error). In other words, we believe that an indurated chronic ulcer existed in each of the 86 cases considered.

The study includes all patients to whom medical advice was given. Nearly half of these patients were advised operation, but insisted on

trying medical treatment. These 86 patients are cases on whom we would have urged operation prior to 1917; they would usually have had gastroenterostomy done and be now in a postsurgical group.

PEPTIC ULCER.

Percentage Results following Hospital Treatment.

G. U.	D. U.	Cases.	Authors.	Years.	Satis- factory.	Im- proved.	No relief.	Oper- ated.	Dead.
4	26	30	Jones	1- 5	60.0				
6	22	28	Shattuck	$\frac{1}{2}$ - 2	78.5		10.7		
	152	152	White	3- 5	57.0	21	4.0	16	
			(many amb.)						
128	342	470	Smithies	2-10	77.0	("Cessation ulcer process")			
	20	20	Blackford	2-10	60.0	15	5.0	15	

Percentage Results following Casual Ambulatory Treatment D. U.

		33	Blackford	5-10	55	12	6	15	12
		27	Blackford	2- 5	63	11	11	4	11
		60	Blackford	2-10	58	12	8	10	12

SUMMARY. RESULTS AFTER TWO TO TEN YEARS. TREATMENT OF PEPTIC ULCER.

(80 Duodenal ulcers: 6 Gastric ulcers.)

86 Medical Cases. (Blackford):	Per cent.
50 Satisfactory	58.1
12 Improved	14.0
7 Unimproved	8.1
9 Operated	10.5
2 Died from ulcer	2.3
6 Died from other causes	7.0

(78 Duodenal ulcers: 25 Gastric ulcers.)

103 Surgical Cases. (Mason):	Per cent.
75 Satisfactory	72.9
15 Unsatisfactory	14.5
8 Excision of ulcer	
7 After gastroenterostomy	
6 Immediate and remote mortality	5.9
7 Deaths from other causes	6.7

Average age:	Years.
Hospital patients	31
Ambulatory patients	41
Whole group	37
Average duration of symptoms:	
Hospital patients	7
Ambulatory patients	12
Whole group	11
Patients over 65 omitted.	

Gastric Ulcer. Only 6 of 44 cases can be included, because the rest have been operated upon in our clinic or by other surgeons. On ambulatory treatment, 3 are practically free from trouble, 2 are somewhat improved, and the other patient, a very old man, is utterly miserable.

Duodenal Ulcer. Eighty cases are available for study; 60 received casual ambulatory treatment and 20 had most careful hospital management and after care as advised by Sippy. Operation was advised for half of the 80 patients, but was refused in favor of a trial on medical management.

Hospital Treatment. Twenty patients show an average age of thirty-one years, with an average history of seven years. Treatment has given satisfactory results in 60 per cent, with some improvement in 15 per cent more. Fifteen per cent have come to operation on account of the failure of medical treatment or of dissatisfaction with it. No relief whatever was obtained in 5 per cent. Seventeen patients out of 20 were treated more than five years ago. One fatality occurred while the patient was taking Sippy treatment, but it is not included here because the patient was not under treatment in the hospital.

Ambulatory Treatment. Sixty patients are available for this study, approximately half treated more than five years ago. Results of follow-up study show that 58 per cent gave satisfactory results, with 12 per cent more who are improved. Eight per cent have had no relief. Ten per cent have come to operation. Twelve per cent are dead.

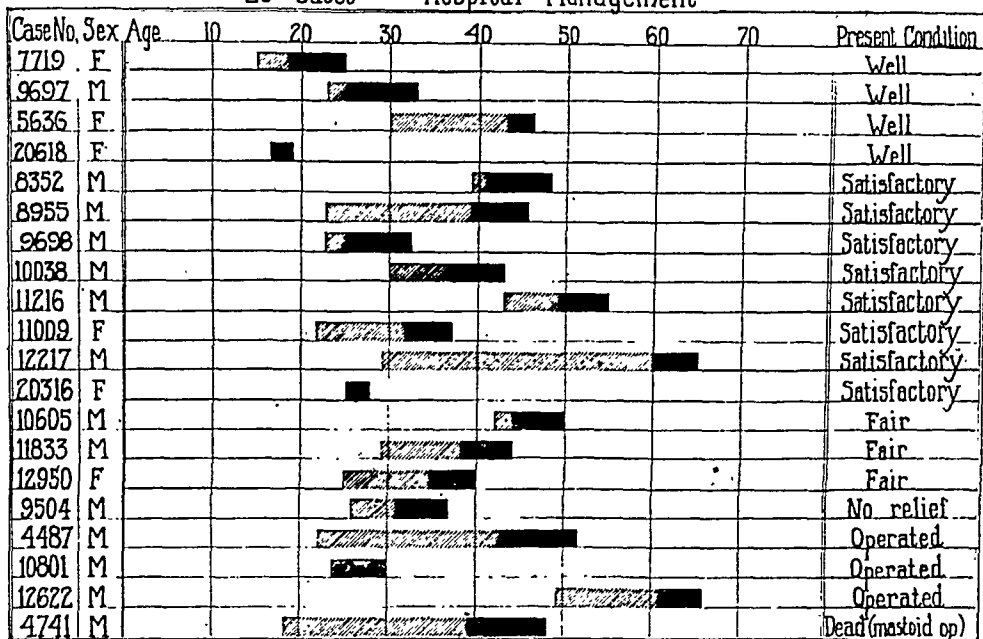
The average age of this ambulatory group is forty-one years, with an average history of disease of twelve years. Thus we see that results in a less favorable class of patients, averaging ten years older and with a history five years longer than those in the hospitalized group, give practically the same percentage of relief as those treated by hospitalization.

Hemorrhages. Massive hemorrhages during or after treatment have occurred in 5 patients, 2 of whom died from hemorrhage.

The first fatality was a man, aged fifty-three years, with a history of duodenal ulcer for many years. Three years before coming to us he had had a successful operation elsewhere for rectal carcinoma. Stomach symptoms forced him to seek relief and he was placed on a Sippy management at home. He died suddenly on the eighteenth day of Sippy treatment from massive hemorrhage. The second fatality was a man, aged eighty-one years, with a history from youth quite typical of duodenal ulcer. He was placed on ambulatory treatment with complete relief for a year. Then prostatectomy was undertaken elsewhere and he died suddenly on the fifth post-operative day from a massive gastric hemorrhage.

Two of the remaining 3 patients had had hospital management.

20 Cases Hospital Management

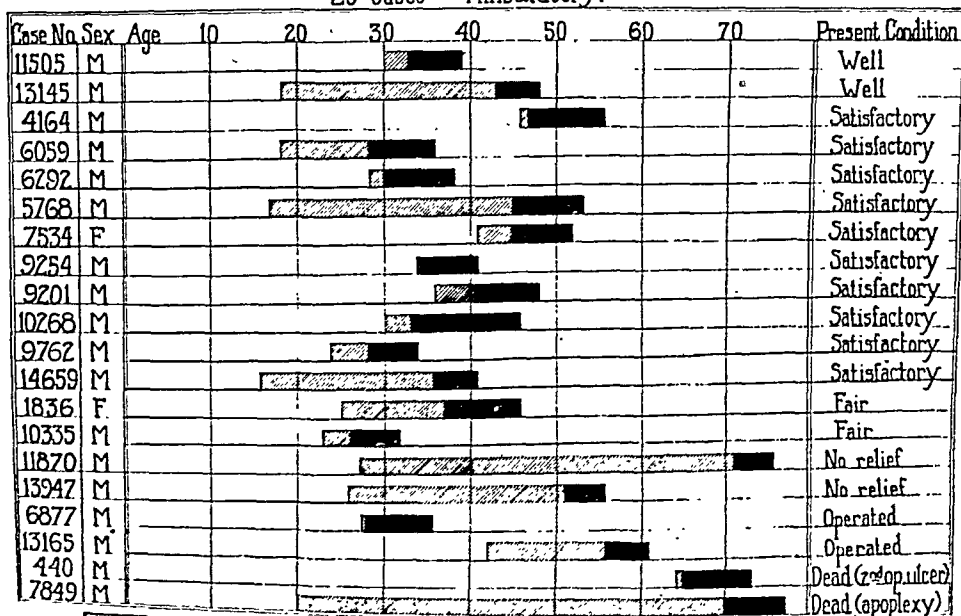


▨ Average duration of symptoms before examination, 7 years.

■ Average period of observation, 6 years.

CHART I.

20 Cases - Ambulatory.



▨ Average duration of symptoms before examination, 12 years

■ Average period of observation, 7 years

CHART II.

Mortality. Nine patients whom we have treated for ulcer are dead. Two died from ulcer hemorrhage, as just related. Seven died from causes not related to ulcer or its complications.

It is worth mentioning that we have had one fatality from an appendiceal abscess which developed years after a gastroenterostomy. Two other patients had hospital medical treatment and subsequently required operation for appendicitis.

Acute Perforation. We have no knowledge that acute perforation has occurred in any patient to whom any kind of medical treatment has been advised.

SURGICAL INDICATIONS. Peptic ulcer with complications is best treated surgically. Obstruction, perforation, repeated massive hemorrhages, extreme pain indicating chronic perforation, and perigastric inflammation are surgical conditions. Recurring attacks of appendicitis or accompanying gall bladder disease are likewise indications for surgery. We have found that most of our gastric ulcer patients have required operation by others if not done by our clinic; hence we have usually advised surgery for gastric ulcer. The laboring man and the unintelligent foreigner suffering from peptic ulcer are usually unable to coöperate in treatment, hence we usually advise operation for them. These ideas, which we believe we share in common with a large part of our profession, have led to operation on most patients suffering from gastric ulcer and on about 40 per cent of patients suffering from duodenal ulcer.

Results of Surgical Treatment. Mason¹⁰ has recently reported results of surgical treatment of peptic ulcer in more than 100 of our patients. His percentage results are practically identical with our medical figures. We recognize immediately, however, that his patients include the patients who had complications, include our bad medical results, and include patients who had had trouble for many years. We can say that the patients operated upon in our clinic average greater severity of symptoms than those treated medically. The surgical results are, therefore, more credit to the surgical treatment.

REMARKS. We feel apologetic about presenting only 20 hospital cases for consideration; yet if we add to them the series reported by Jones² and that reported by White,⁴ we have 200 cases, with identical percentage results; and 200 patients make a group large enough to allow at least some conclusions to be drawn. We believe that 60 cases followed after ambulatory treatment are a sufficient number to permit us to draw conclusions.

Though not a constant procedure, we have reëxamined many of our patients. We have repeatedly confirmed the now well-known fact that most clinically cured ulcers still show Roentgen ray findings typical of ulcer.

Mortality from causes not related to ulcer is no reason to presume the failure of ulcer treatment. If 70 per cent of the reported 9 deaths

were added to 60 per cent of good results and 10 per cent of cases reporting improvement, then we can state that 7 per cent plus 10 per cent plus 60 per cent gives 77 per cent in which medical treatment has been justified—and some statistics have been thus built up.

There are no figures on what happens to untreated peptic ulcer, but undoubtedly many ulcers are unrecognized and yet their possessor lives to old age. The physician sees only the patients having enough trouble to bring them to him for relief.

The evaluation of results in a follow-up study is after all the patient's interpretation of results, whether he has been treated surgically or medically.

CONCLUSIONS. These observations after a period of two to ten years have shown:

1. Casual ambulatory medical treatment has been satisfactory in 60 per cent of uncomplicated cases of duodenal ulcer.

2. Careful Sippy management has likewise been satisfactory in 60 per cent.

3. Hospital medical treatment has not given better results than ambulatory treatment. Hospital treatment may better train the patient to look after himself, yet the results have not been better for the patient.

4. Serious hemorrhage during or after medical treatment has occurred in 6 per cent (5 out of 80 cases).

5. No instance of perforation is known to have occurred during or after any kind of medical advice.

6. A mortality of 2 per cent (2 cases) attributable to ulcer hemorrhage has occurred in follow-ups for from two to ten years. Both cases were notably poor risks that would not have been considered surgical by the most enthusiastic surgeon.

7. Hemorrhages have not been prevented by either medical or surgical treatment. They have occurred after medical or surgical treatment with the same percentage of frequency. Repeated hemorrhages indicate a resection of the ulcer-bearing area.

8. Complications of peptic ulcer are best treated surgically. Such cases give the best surgical results and the poorest medical results.

9. Our medical cases cannot be considered to parallel in severity the surgical cases. The surgically treated ulcer cases include the bad medical results, the complications, and the very severe cases.

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THE EFFECT OF SMALLER DOSES OF HISTAMIN IN STIMULATING HUMAN GASTRIC SECRETION.*

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HISTAMIN has been demonstrated beyond question to be a stimulant to gastric secretion; and experiments have shown further that this drug may be used as a possible aid in differentiating between true and pseudoachylia.¹ Since 1925, many contributions have appeared in the literature on the subject and its related phases.

A review of the experiments dealing with the action of histamin on man shows that in practically all of the tests hitherto conducted, the dosage employed has ranged from 1 mg. to 1.50 mg. or more. That these quantities may be unduly large is suggested by the reports of unpleasant or even severe reactions following the subcutaneous injections of the doses used.

Accordingly, we deemed it important to ascertain whether the dosage of histamin could be diminished so as to avert unpleasant symptoms or at least reduce them to a minimum without entirely impairing the efficacy of histamin as a gastric stimulant. This seemed the more important because no attempt appears to have been made hitherto to determine precisely within what ranges effective dosage lies.

In the present study, emphasis has been placed upon the dosage factor rather than upon other features of the secretory response of man to histamin hydrochlorid.

The human subjects selected for observation averaged 160 pounds in body weight. Each subject reported in the morning before breakfast, so that the fasting stomach contents could be extracted. Particular attention was devoted to any systemic reactions that could be detected. A record was taken of blood pressure and pulse rate. The subjects were then given subcutaneous injections of histamin, whereupon the observations of blood pressures and pulse rate were further taken at the end of five, ten and fifteen minutes; and thereafter at fifteen-minute intervals. Simultaneously samples of gastric contents were removed by the aid of an Einhorn or Rehfuess tube at fifteen-minute periods. The material thus removed was measured; the free hydrochloric acid and total acidity determined and expressed in terms of cubic centimeters of tenth normal acid. Furthermore, the total volume of the secretion during

* Read before American Gastro-enterological Association, May 1, 1928, Washington, D. C.

the intervals was also ascertained. The subjects were not permitted to swallow saliva and were made to expectorate into vessels designated for such purpose. Some subjects were also given a standard test meal of one shredded wheat biscuit and 200 cc. of water. This

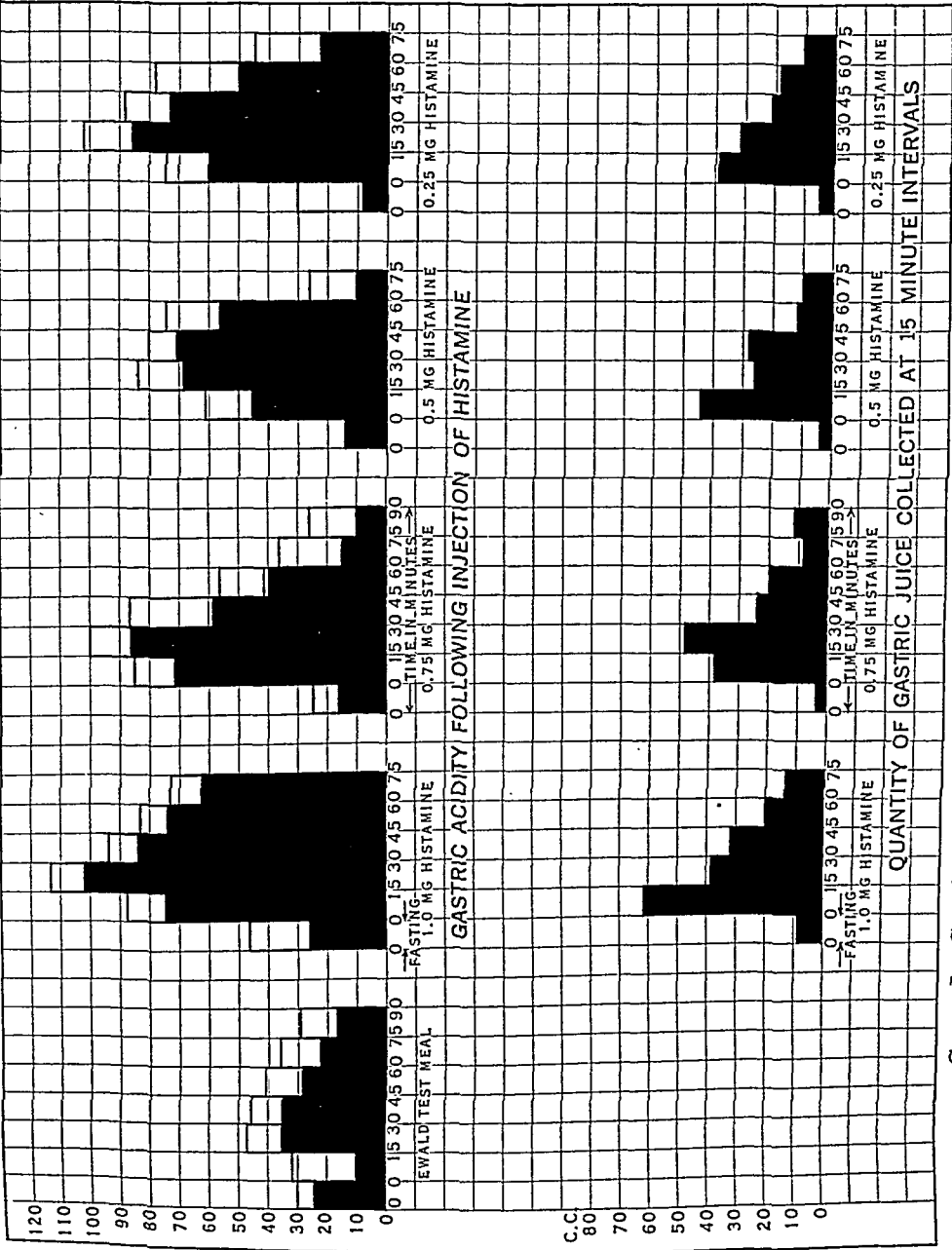


CHART I.—Gastric response to subcutaneous injections of histamin. Subject A.

was done to compare gastric secretion on the same individual when no drug was given.
The preparation of histamin employed was the commercial Imido-Roche 1 cc. (1:1000) = 1 mg. introduced in dosages of 1 mg.,

0.75 mg., 0.50 mg., and 0.25 mg., respectively. Following the 1-mg. dose, and within five minutes after injection there developed a marked erythema of the face, neck and upper part of the thorax

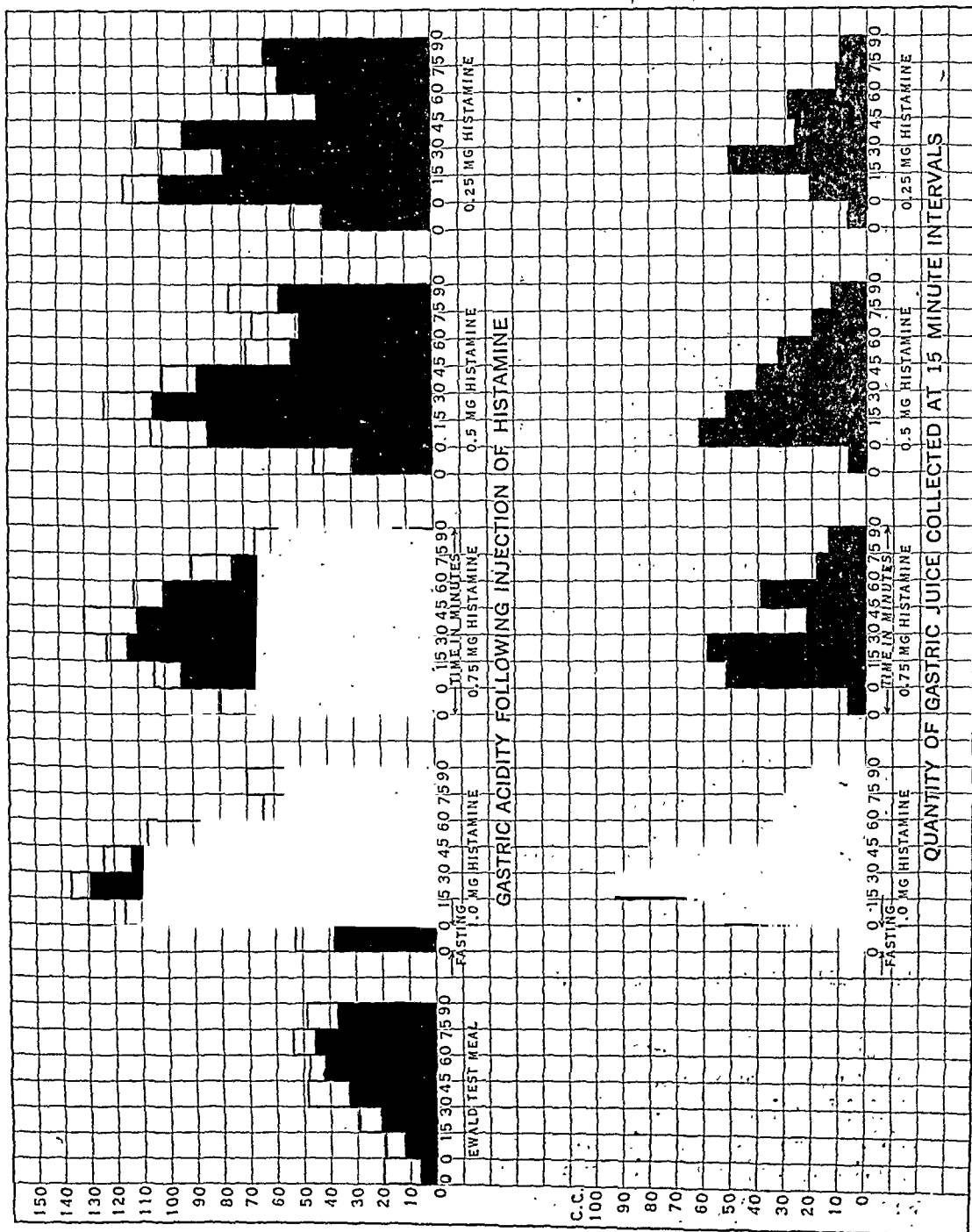
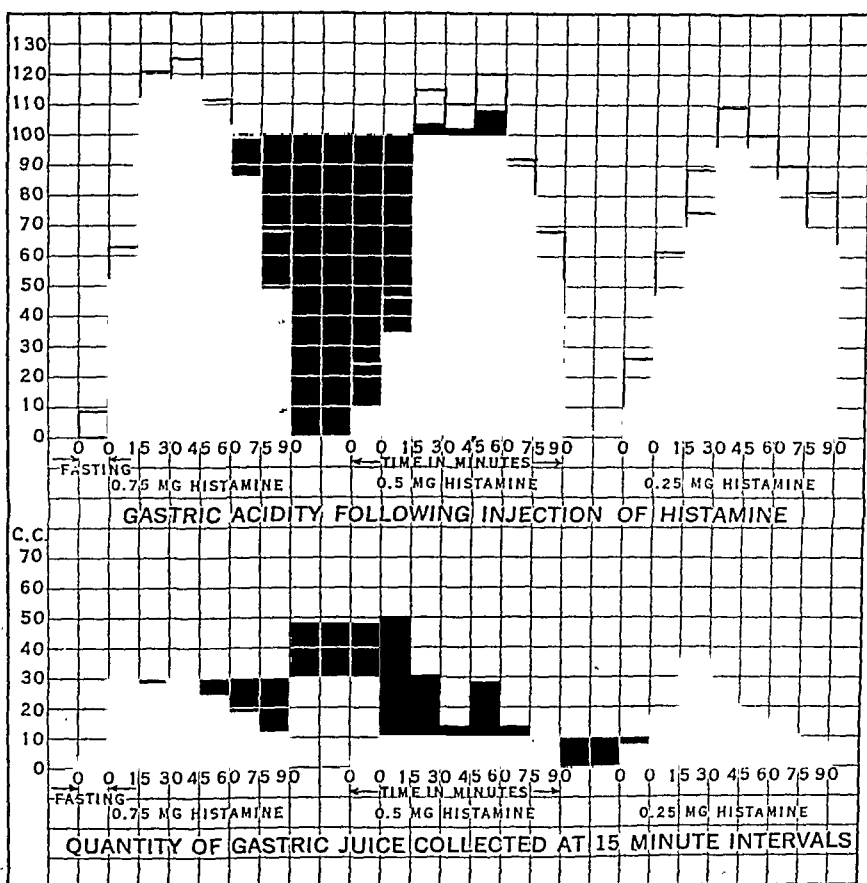


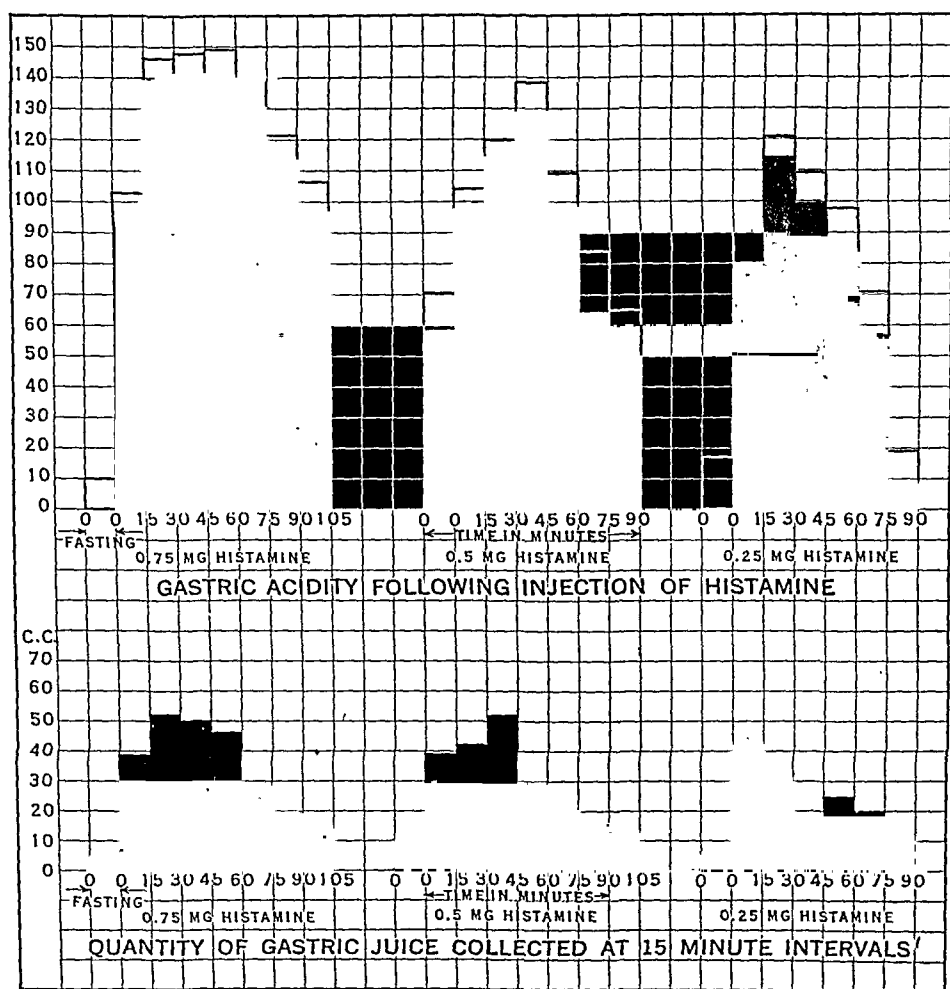
CHART II.—Gastric response to subcutaneous injections of histamin. Subject B.

which persisted for about forty-five to fifty minutes. Also, at the site of injection, there appeared an elevated white wheal, irregular in outline measuring about 5 cm. in diameter, surrounded by a large

area of erythema and accompanied by an itching and stinging sensation. This local reaction at the site lasted about forty-five to sixty minutes and in every instance there was a flushing of the face, a feeling of intense warmth, and heaviness and throbbing sensations in the head, particularly in the temples. Watering of the eyes and increased salivation also were noted. The maximum intensity of symptoms occurred from fifteen to twenty minutes after injection and then gradually diminished during the periods indicated.



None of the four dosages just mentioned gave rise to any appreciable difference in the pulse rate or blood pressure, except that in some instances the former increased at most 10 beats while the blood pressure fell about 10 mm. (see table). Even with the smaller doses referred to, histamin remains potent as a gastric stimulant in confirmation of our earlier observations on the effect of this drug. In every instance, there was promotion of gastric secretion and acidity



THE SYSTEMIC EFFECTS AND GASTRIC SECRETORY RESPONSE PRODUCED IN THE SAME INDIVIDUAL BY DIFFERENT DOSES OF HISTAMIN.

Time.	Blood pressure.				Pulse rate.				Vol. secretion.				Free HCl.				Total acidity.			
	1	mg. .75	.50	.25	1	mg. .75	.50	.25	1	mg. .75	.50	.25	1	mg. .75	.50	.25	1	mg. .75	.50	.25
Fasting	110	100	112	100	68	72	64	72	20	cc. 4	8	30	24	14	0	6	40	24	14	30
Injection of Histamin	76	74	66	60																
5 min.	106	90	110	90	70	82	68	72												
10 min.	62	60	74	60																
	104	90	108	100	76	82	70	60												
15 min.	60	60	60	70																
	100	94	104	100	76	66	64	68	60	35	12	38	74	70	44	60	86	84	62	74
30 min.	60	60	66	64																
	100	96	106	102	64	66	66	68	35	45	23	32	102	86	68	84	114	100	82	102
	66	66	70	66																
45 min.	104	94	108	100	70	64	66	68	12	22	25	20	84	74	70	72	94	86	80	86
	74	68	72	70																
60 min.	106	100	108	98	70	64	64	70	12	18	10	18	74	40	54	52	84	36	74	78
	76	70	80	68																
75 min.	108	100	110	100	70	64	64	66	8	10	8	10	62	14	8	22	74	28	26	44
	78	74	76	72																

Conclusions. It is here shown that as little as 0.25 mg. of histamin hydrochlorid suffices to demonstrate its action as a gastric secretory stimulant. This dose is devoid of untoward effects or any unpleasant symptoms whatever. Accordingly the previously recommended larger dosage (0.50 mg.) no longer seems necessary nor desirable in diagnostic or therapeutic procedures.

The determination of the minimum effective dose of histamin for producing an unmistakable functional response of the gastric glands has paved the way for a consideration of the possible use of the drug for therapeutic purposes in appropriate cases of impaired gastric secretory function. With the effective dosage thus reduced to a minimum, the production of objectionable systemic effects is practically averted.

Histamin hydrochlorid in 0.25-mg. doses appears to be useful in all conditions where a safe and efficient gastric stimulant is indicated.

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OBSERVATIONS ON PEPTIC ULCER. VI. PRELIMINARY REPORT OF CLINICAL EXPERIMENTS WITH GASTRO- DUODENAL ANALYSIS.

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IN several previous papers²⁻⁶ I have reported the experimental production and healing of subacute and chronic peptic ulcers in the stomach, duodenum and jejunum of dogs. Both grossly and microscopically these ulcers were indistinguishable from the peptic ulcers encountered clinically in the stomach and duodenum of man. Furthermore, they always occurred in the same locations in the stomach and intestine of the experimental animal that most frequently harbor peptic ulcer in man, namely, the lesser curvature of the stomach and the first portion of the duodenum just distal to the pylorus.

An analysis of the factors involved in the experiments on dogs demonstrated that the formation of typical peptic ulcers followed the withdrawal of alkali from the stomach and intestine into which it emptied and the site of the ulcer in each case was determined by the point at which the forces exerted by the stomach in ejecting the acid chyme converged. Healing of the ulcers ensued when measures were taken to reintroduce alkali into the region of the ulcer or when the forces of the acid ejections of the stomach were diffused or counteracted.

The data of the experiments suggested the probable presence in the normal dog of some relative balance at the pylorus between the acidity of the stomach and the alkalinity of the duodenum. Because of the close similarity in every respect between the experimentally produced peptic ulcers and the peptic ulcers encountered in man, I conceived the following series of experiments on groups of patients free from peptic ulcer and those having peptic ulcer. For convenience, the technique of the experiments to be described was given the name "gastroduodenal analysis."

While the series is not large, the constancy of the results in each group seemed to justify this communication which is presented as a preliminary report.

Methods of Experimentation. The simplest means of determining the relative concentrations of acid and alkali in the stomach and duodenum seemed to be by the passage of tubes into the stomach and duodenum respectively and the withdrawal of samples of their contents for titration.

The technique employed was as follows: As in ordinary gastric analyses, no food was given the patient during the night preceding

the morning of the test. With the patient in the sitting posture a soft graduated, Rehfuß tube was passed into the stomach, this point being indicated by the first mark on the tube. The patient was then made to lie on the right side and the tube was passed farther until the second mark was almost reached. About twenty minutes was then consumed in passing the tube as far as the third mark which indicates the length of the tube necessary to lodge the metal tip in the duodenum. In some cases the passage of the tube through the pylorus seemed to be facilitated by allowing the patient a swallow of water at the time the metal tip was in the region of the pylorus.

After the duodenal tube had been passed the patient was allowed to eat the usual Ewald test meal consisting of two slices of bread without the crust and a glass of water. In order to make sure that the end of the tube remained in the duodenum the patient was kept lying on the right side for the entire period of the test.

For the withdrawal of material from the stomach, a second Rehfuß tube was passed into the stomach. In this way samples of their contents could be withdrawn from both the stomach and the duodenum simultaneously at any time after the ingestion of the test meal. For the withdrawal of samples ordinary glass syringes of 25-cc. to 50-cc. capacity were used.

In order to have accurate information as to the exact position of the tubes in the stomach and duodenum, fluoroscopic examinations were made during the course of every experiment. In all cases, the tubes and their metal tips were well depicted by the Roentgen rays. In some experiments, roentgenograms were made (Fig. 1).

Samples withdrawn from the stomach and duodenum were carefully labeled as to their source and the time of their withdrawal. They were titrated within a few minutes after their withdrawal.

The simplest method of titration proved to be the same as that usually employed in the ordinary examination of contents from the stomach. The material to be tested was measured and a tenth normal solution of sodium hydroxide (NaOH) used for titration. Dimethyl-amino-azo-benzol and phenolphthalein were used as indicators for the free hydrochloric acid (HCl) and the total acids respectively. The results were expressed in terms of "acidity per cent," the method commonly employed for recording gastric acidity.

Results. General Observations. In most cases the patients did not object to the passage of two Rehfuß tubes. In some experiments the tubes were left in place for as much as two hours without discomfort.

The passage of a tube into the duodenum was usually evidenced by the character of the material which could be withdrawn from the tube in small amounts. This was a yellow fluid which seemed to contain large quantities of bile. It contrasted sharply with the cloudy, white material characteristic of the contents of the stomach.

In some experiments in which the tube for passage into the duodenum did not pass the pylorus in the usual way, the Ewald test

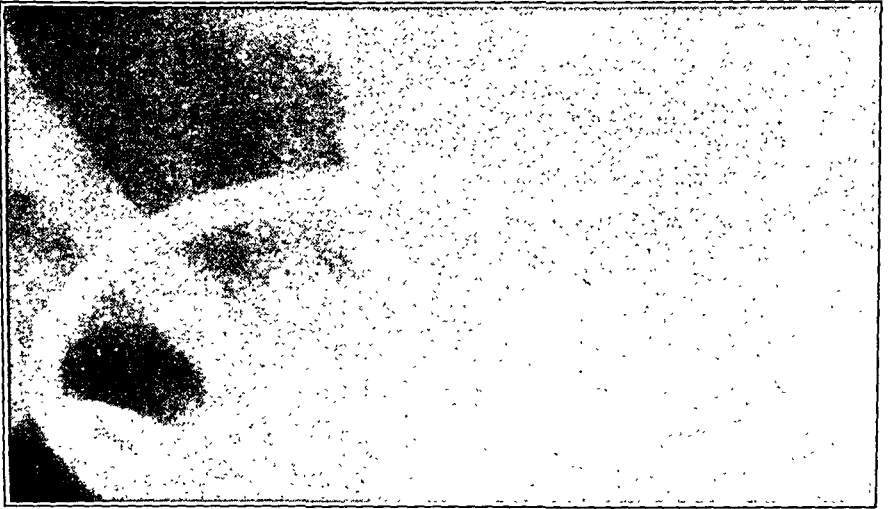
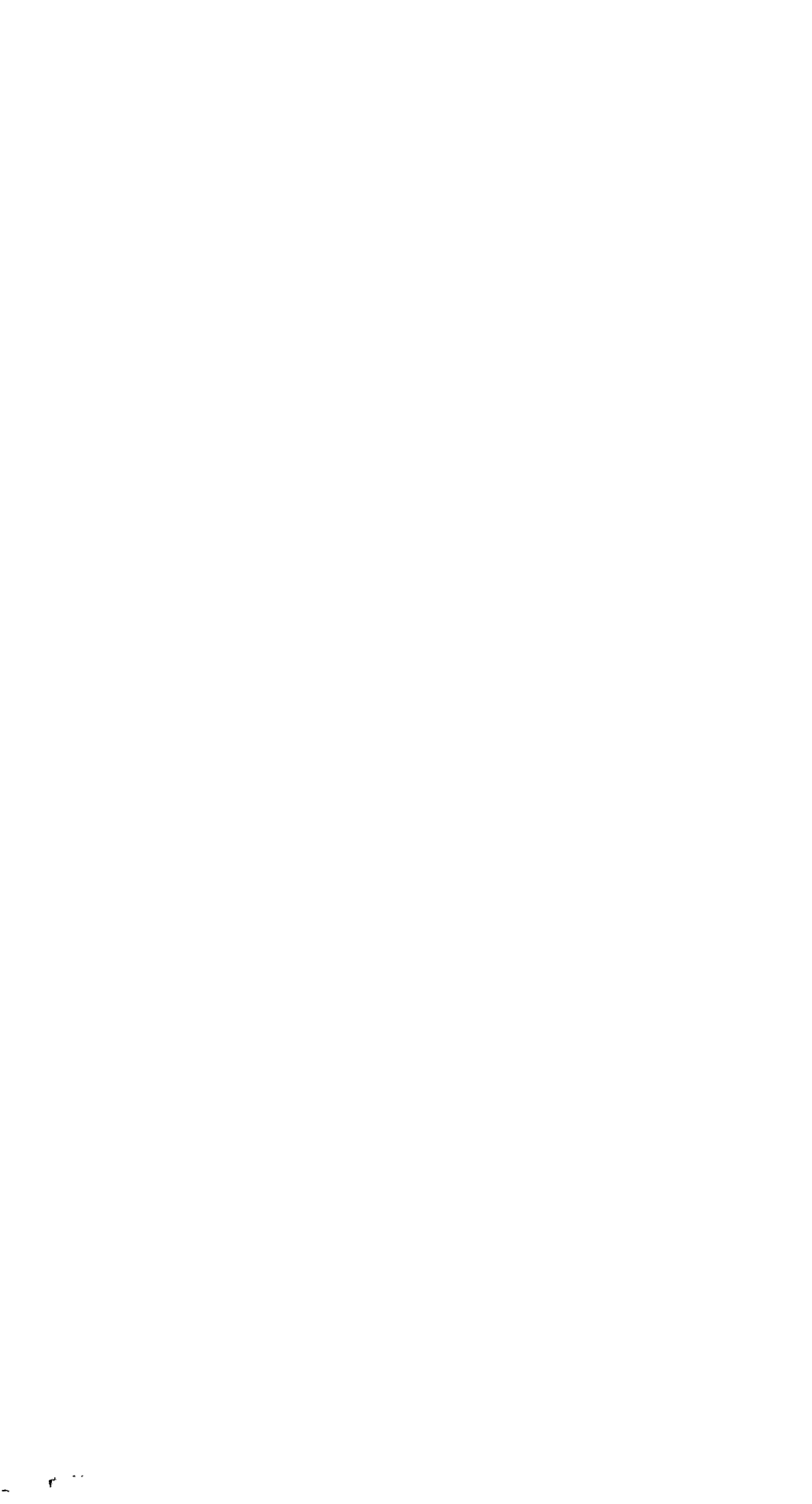


FIG. 1.—The metal tip of the first tube is in the duodenum just beyond the pylorus
The metal tip of the second tube is in the upper part of the stomach.



meal was given with the patient lying on the right side and as the digested portions of the meal entered the duodenum the tip of the Rehfuß tube accompanied them.

Chyme could be withdrawn from the stomach in an almost continuous stream, the total amount being determined only by the total volume of chyme in the stomach. Material from the duodenum, however, could be withdrawn only in small amounts at one time and seemed to come in periodic spurts as though representing cyclic ejections of chyme from the stomach.

In some instances, the fluoroscopic examination revealed the tip of the duodenal tube lodged in the stomach just on the gastric side of the pylorus. Material withdrawn from tubes in this location was very similar in appearance to that usually obtained from the duodenum. The acidity of such samples was higher than that of the contents of the duodenum but lower than that of the gastric chyme.

Observations on Persons without Peptic Ulcer. For the experiments of this group, two types of patients were selected: For the first, those who had no complaints, symptoms or signs referable to the abdomen or gastrointestinal tract (Table I), for the second, those who complained of pains in the abdomen but who did not have any symptoms or signs of peptic ulcer (Table II).

Gastroduodenal analyses were made satisfactorily in 13 persons who did not have a peptic ulcer. Of this number 5 were normal except for slight wounds of the extremities. Of the remaining 8, 3 had gastric neuroses, 1 had chronic appendicitis, 2 had cholecystic disease, 1 had gastric achlorhydria, and 1 had pyloric achalasia, a spasmodic narrowing of the pylorus with inability to relax properly. In all of the patients the first tube passed into the duodenum with relative ease except in the case of the patient with pyloric achalasia in whom several attempts were made on successive days before the tube finally passed the pylorus.

Examination of the contents of the stomach in these 13 persons showed a wide variation in the concentrations of the free hydrochloric acid and the total acids. This was true in both the normal patients and those with abdominal symptoms from diseases other than peptic ulcer. In spite of this wide variation in the acidity in the stomach the acidity of the duodenal contents was always low and relatively constant.

Of this group of 13 patients that did not have peptic ulcer the most constant feature was the complete absence of free hydrochloric acid in the material withdrawn from the duodenum. The only exception in the group was in the case with pyloric achalasia.

Observations on Persons with Peptic Ulcer. Gastroduodenal analyses were attempted in 23 patients with peptic ulcer. It was impossible to get a duodenal tube past the pylorus in more than 8 of this number, although two or more attempts were sometimes made.

TABLE I.—GASTRIC AND DUODENAL ACIDITY. NORMAL PATIENTS. NO ABDOMINAL COMPLAINT.

Patient.	Age.	Diagnosis.	Titration in "acidity per cent."				Time interval between test meal and its withdrawal.	Remarks.
			Stomach		Duodenum.			
			Free HCl.	Total acids.	Free HCl.	Total acids.		
Miss L. S.	16	Laceration, hand	0°	7°	$\frac{1}{4}$ hr.	
			0°	20°	$\frac{1}{2}$ hr.	
			10°	25°	0°	6°	1 hr.	
			33°	68°	0°	8°	1 hr.	
Mr. R. S.	21	Burn, knee	18°	28°	0°	10°	1 hr.	
Mr. T. T.	19	Wound, knee	35°	135°	0°	18°	1 hr.	
Mr. L. C.	18	Laceration, foot	28°	64°	0°	35°	1 hr.	
Mr. M. J.	19	Wound, leg						

TABLE II.—PATIENTS WITH ABDOMINAL COMPLAINTS BUT WITHOUT PEPTIC ULCER.

Patient.	Age.	Diagnosis.	Titration in "acidity per cent."				Time interval between test meal and its withdrawal.	Remarks.
			Stomach		Duodenum.			
			Free HCl.	Total acids.	Free HCl.	Total acids.		
Mr. J. S.	21	Gastric neurosis	50°	70°	0°	10°	1 hr.	Roentgenologic examination of stomach, etc., negative.
Mr. M. H.	67	Gastric neurosis	58°	66°	0°	15°	1 hr.	Roentgenologic examination of stomach, etc., negative.
Mr. R. B. B.	23	Gastric neurosis	32°	44°	0°	12°	1 hr.	Roentgenologic examination of stomach, etc., negative.
			0°	6°	1½ hrs.	
Mr. E. J.	47	Chronic appendicitis	44°	74°	0°	10°	1 hr.	Roentgenologic examination of stomach, etc., negative.
Mrs. C. M.	36	Chronic cholecystitis	15°	30°	0°	12°	1 hr.	Diagnosis verified at operation.
Mr. R. B.	53	Solitary cholelithiasis	40°	60°	0°	20°	1 hr.	Roentgenologic diagnosis.
Mr. E. L.	70	Achlorhydria gastrica	0°	15°	0°	10°	1 hr.	Roentgenologic and laboratory diagnosis. Exploratory laparotomy refused.
Mr. C. T.	42	Pyloric achalasia	30°	55°	14°	25°	1 hr.	Roentgenologic diagnosis, verified at operation.

TABLE III.—PATIENTS WITH PEPTIC ULCER.

Patient.	Age.	Diagnosis.	Titration in "acidity per cent."				Time interval between test meal and its withdrawal.	Remarks.								
			Stomach		Duodenum.											
			Free HCl.	Total acids.	Free HCl.	Total acids.										
Dr. M. W. Mr. G. P.	25	Duodenal ulcer	44°	56°	14°	30°	1 hr.	Clinical and roentgenologic diagnosis.								
	39	Duodenal ulcer	43°	52°	13°	22°	1 hr.	Clinical and roentgenologic diagnosis.								
	Mr. L. S.	31	Duodenal ulcer	{ 57°	77°	$\frac{1}{2}$ hr.	Clinical and roentgenologic diagnosis.							
42°				53°	1 hr.									
{	1 $\frac{1}{4}$ hr.									
Mrs. B. B.	26	Duodenal ulcer	{ 33°	52°	10°	40°	1 hr.	Clinical and roentgenologic diagnosis.								
			20°	47°										
			13°	36°										
Miss R. P.	52	Duodenal ulcer	{ 29°	46°	5°	16°	1 $\frac{1}{4}$ hrs.	Clinical and roentgenologic diagnosis.								
			84°	92°	26°	36°	1 hr.									
			7°	17°	2°	14°	1 hr.									
Dr. J. K.	..	Duodenal ulcer	{ 5°	20°	0°	18°		Clinical and roentgenologic diagnosis.								
			2°	4°	0°	0°										
			Mrs. P. G.	67	Gastric ulcer; cancer?	15°	24°		3°	20°	1 hr.	Clinical and roentgenologic diagnosis. laparotomy refused.				
Mrs. P. W.	32	Gastric ulcer														Clinical and roentgenologic diagnosis. laparotomy refused.

Exploratory

Exploratory

Of the 8 patients in whom gastroduodenal analysis was accomplished, 6 had ulcer of the duodenum and 2 had ulcer of the stomach (Table III). As in the preceding group of patients, the acidity of the contents of the stomach varied widely. The acidity of the duodenal contents showed wider variations and was in general higher than in the patients who did not have peptic ulcer.

The most constant feature of this group of 8 patients with peptic ulcer was that all except 1 showed the presence of free hydrochloric acid in the samples of duodenal contents. In this case, the gastric acidity was very low.

Discussion. Both the experimental and clinical data on peptic ulcer seem to suggest that the site of ulceration is determined by mechanical factors. The trauma administered to the mucosa by the propelling of food along the lesser curvature and the ejection of food from the nozzle-like pylorus against the wall of the duodenum offers a plausible explanation for the usual occurrence of peptic ulcer in these locations.

The data of previously reported experiments on dogs suggested that the chronicity of peptic ulcer might be due to a relative imbalance between the acids of the stomach and the alkalies of the duodenum with a resulting preponderance of the acid.

Many workers have linked gastric hyperacidity with peptic ulcer but so many cases of hyperacidity were found without peptic ulcer and so many cases of peptic ulcer occurred without hyperacidity that the usual type of gastric analysis offered little or no aid in studying the etiology of peptic ulcer or in diagnosing the disease. This fact is illustrated by the wide variations in the gastric acidity of the patients in these experiments.

It is generally believed that the alkalies of the duodenum, the bile, pancreatic juice, and duodenal secretion, neutralize the acids of the stomach during digestion. Partial neutralization takes place in the pyloric portion of the stomach by regurgitation of secretions from the duodenum and neutralization is completed after the gastric chyme enters the duodenum.

The experiments on patients without peptic ulcer seem to substantiate this belief. Regardless of the variation in the concentration of acid in the stomach neutralization occurred in the duodenum and samples of material withdrawn from the duodenum showed no free hydrochloric acid and only a small but fairly constant concentration of total acids. After the completion of these experiments a reference was found to the work of Baird, Campbell and Hearn.¹ In experiments of a somewhat similar nature, they investigated the acidity of the duodenum in normal persons only. They obtained results similar to my own in normal persons. They did not investigate any patients with peptic ulcer.

In my experiments the absence of free hydrochloric acid in the duodenum occurred only in those patients who did not have peptic

ulcer. In those who did have peptic ulcer neutralization was not complete and samples of material withdrawn from the duodenum showed the presence of free hydrochloric acid and a considerable range of variation in the concentration of total acids.

The experiments suggest, therefore, the presence of a relative acid-alkali balance between the secretions of the stomach and duodenum in normal individuals and a relative acid-alkali imbalance in those persons with peptic ulcer.

Such an imbalance might be produced in several ways: by a hypersecretion of acid, by a hyposecretion of alkali, by a combination of the two, or by improper functioning of the pylorus, thereby preventing the normal interchange between the contents of the stomach and duodenum. The importance of the last factor is suggested by the difficulty encountered in passing a tube through the pylorus in the experiments on all persons with peptic ulcer and by the atypical findings in the experiment in which pyloric achalasia was present.

Provided the data of these experiments can be verified in a larger series of cases it seems probable that they may help to clarify the problem of the etiology of peptic ulcer. The site of ulceration may be attributable to mechanical factors and the chronicity of the ulcer to insufficient or improper neutralization of the acid gastric chyme caused by altered physiologic processes. Furthermore gastroduodenal analysis may find some application as a measure to assist in the diagnosis of peptic ulcer.

Summary. Some of the author's previously reported experiments with the production and healing of peptic ulcers in dogs are briefly reviewed. The experiments suggested the importance of mechanical and chemical factors in determining the location and chronicity of the peptic ulcers.

In a preliminary report some experiments are described in which tubes were passed into the stomach and duodenum in two groups of patients: those without peptic ulcer and those with peptic ulcer. The position of all tubes was verified roentgenologically. Ewald test meals were eaten by the patients and afterward samples of material were withdrawn from the stomach and duodenum simultaneously.

In persons without peptic ulcer, no free hydrochloric acid was recovered in samples of the contents of the duodenum. In persons with peptic ulcer, free hydrochloric acid was found in samples from the duodenum. The experiments on patients suggested the presence of a relative acid-alkali balance between the secretions of the stomach and duodenum in normal persons and a relative acid-alkali imbalance in those persons with peptic ulcer.

An analysis of the factors involved in these and previous experiments suggested the probability that the site of peptic ulcer is determined by mechanical factors and that the chronicity may be due to a relative imbalance between the acids of the stomach and

the alkalies of the duodenum, causing incomplete or faulty neutralization of the acid gastric chyme. Improper functioning of the pylorus may be an important factor in causing the acid-alkali imbalance.

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THE EXTENT OF THE VARIATIONS IN THE LEUKOCYTES OF NORMAL INDIVIDUALS.

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THE value of the leukocytic formula in any pathologic condition depends very largely upon its variation from the normal. To evaluate any pathologic formula when followed over a considerable period of time it would appear necessary to establish the variation of the leukocytes in normal individuals over a relative period. From a survey of the literature it seems that but little work has been done on this particular phase in studies of the leukocytes. The reports made have been on a few individuals studied under especial conditions and have been made very largely on the male sex.

For the past two years the leukocytic reactions in tuberculous cases of both sexes have been followed by weekly counts taken at relatively the same time of day and on the same day of the week. To establish a normal as a basis for comparison of these studies a group of 17 average normal individuals was followed for a period of eleven weeks. The present report gives the data obtained from the blood counts on the normal group.

The group studied consisted of 9 adult males and 8 adult females. The age range in the male was from eighteen to forty years, and in the female from twenty-four to fifty-two years. Every case was examined physically and roentgenograms of the chest were made

to rule out any evidence of active pulmonary disease. It is almost impossible to get a sufficient number of perfectly normal chests, by Roentgen ray, for study, so that this group contains what may be called the average "normal" chest. The group proved to be in good health, as but two counts were missed on account of disabling illness—both acute upper respiratory infections.

The main point in the problem was to get the extent of the leukocytic variation among a group of healthy people pursuing their usual mode of life. It was desired to get the greatest variation normal individuals might show. It was felt that people residing in a large city lived a more strenuous life than those residing in a rural setting, consequently New York City was chosen as the place where normal individuals would lead the most hectic existence. Physicians and nurses always lead a life of great irregularity and are more constantly in contact with individuals suffering from all types of infection than any other group of normal individuals, therefore the individuals taken for this study were all from the medical division at the Home Office of the Metropolitan Life Insurance Company. Statistics show that there occurs a larger number of acute infections, respiratory infections in particular, in New York City in January, February and March than at any other time of the year, so that this period of the year was deliberately chosen to carry on the study. In brief, the conditions under which the study was made were such that one would expect to get the greatest variation that was consistent with health. It is of course recognized that similar studies of normal individuals in a different environment might easily give considerably different averages and extremes.

Method. All of the total and differential counts and the obtaining of the blood samples were done by the author. The morning samples were obtained between 9.30 and 10.15, except where noted to the contrary, and the afternoon samples were obtained between 2.30 and 3.15. Two individuals had afternoon counts throughout the study. In 11 the examinations were all made in the morning, and in 4 cases morning examinations were made the first six weeks and afternoon examinations thereafter. Weekly counts, on Friday of each week, were done for ten weeks. For the last week of the study daily counts were made for five days. In all, 241 counts out of a possible 247, were done. In each individual a careful record was kept of "head colds" and any other minor ailment, and in the females a careful record of the menses, without the knowledge of the author until the study had been completed.

The following technique has been used in all counts. It has been found to give consistent results and is as simple as possible when one desires a fair degree of accuracy. Another method may give greater accuracy but it is felt that the value of any technique lies in the rigid adherence to a routine procedure when it has been found to give consistent results.

All diluting pipettes and double Levy counting chambers used in this study have been certified by the United States Bureau of Standards. The same pipettes and counting chambers have been used in the counting of over 4000 samples of blood and have been found to be accurate within small variations.

The blood for the total counts has all been diluted twenty times. The pipettes have been vigorously shaken two minutes at the time the blood was taken, and three minutes more before being placed in the counting chamber. Two samples from the pipettes were placed in the double counting chamber. At least 2 drops of the diluted blood was discarded between the two samples. Two large squares, diagonally opposite, were counted in each chamber and the average of the four squares was taken for the total count.

The blood smears were made on cover glasses. The cover glasses were moved across the drop of blood to be examined so that a line of blood 1 to 2 mm. wide was obtained. In this way the blood spreads in a straight line, not in a circle.

All smears have been stained with Wright's blood stain. In all differentials 400 cells have been counted. The high dry objective and a No. 10 ocular have been used instead of a higher magnification.

No attempt has been made to classify the lymphocytes into groups of the large and small type. All cells which had a finely granular, muddy blue cytoplasm have been classed as large mononuclear leukocytes, regardless of the shape of the nucleus. The nucleus in this cell may be round, oval, bean-shaped, horse-shoe shaped, or considerably lobulated. The usual grouping of the granulocytic series has been followed.

Results. The following is the record of the counts and other data on each of the individuals:

GROUP I.—LEUKOCYTE AND DIFFERENTIAL COUNTS—(ALL COUNTS BETWEEN 9.30 AND 10.15 A.M.).*

1. Dr. E., female, aged twenty-eight years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.	
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.		
1-6	8100	58.0	4700	32.0	2600	8.0	650	1.5	120	0.5	40	Menses.	
1-13	6800	46.0	3100	40.0	2700	8.0	540	5.0	340	1.0	70		
1-20	6800	49.0	3300	34.0	2300	11.0	750	5.0	340	1.0	70		
1-27	5400	48.0	2600	39.0	2100	9.0	490	3.0	160	1.5	80		
2-3	6400	48.0	3100	35.0	2200	11.0	700	4.5	290	1.5	100	Coryza.	
2-10	5400	48.0	2600	28.0	2000	8.0	430	3.0	160	2.0	90		
2-17	6700	47.0	3100	36.0	2400	11.0	740	4.0	270	2.0	130		
2-24	5200	47.0	2400	35.0	1800	9.0	470	8.0	420	1.0	50	Menses.	
3-2	5200	38.0	2000	44.0	2300	11.0	570	6.0	310	1.0	50		
3-9	Absent	—sinus infection											Still considerable discharge from sinus.
3-15	9100	54.0	4900	30.0	2700	10.5	950	5.0	450	0.5	40		
3-16	6500	67.0	4400	21.0	1400	6.0	390	5.0	320	1.0	60		
3-19	7300	56.0	4100	29.0	2100	10.5	770	3.5	250	1.0	70		
3-20	8000	49.0	3900	35.0	2800	11.0	880	4.5	360	0.5	40	Menses.	

* The total cells in all of the charts are accurate to within 100 cells for the neutrophils and lymphocytes and within 10 cells for the other cell types.

2. Dr. H., male, aged thirty-eight years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	5,400	47.0	2500	40.0	2100	9.0	480	4.0	220	0		
1-13	6,300	55.0	3500	32.0	2000	10.0	630	2.0	130	1.0	60	
1-20	6,000	55.0	3300	33.0	2000	11.0	660	1.0	60	0		
1-27	10,200	55.0	5600	33.0	3400	10.0	1020	2.0	200	0		Coryza.
2-3	8,000	45.5	3600	40.0	3200	12.0	960	1.5	120	1.0	80	
2-10	7,400	56.0	4100	34.0	2500	8.0	590	1.5	110	0.5	40	
2-17	5,400	55.0	3000	32.0	1700	10.0	540	2.5	130	0.5	30	Coryza.
2-24	5,600	46.5	2600	41.0	2300	10.0	560	2.0	110	0.5	30	
3-2	6,100	52.0	3200	36.0	2200	9.5	580	2.0	120	0.5	30	Bad tracheitis for 2 days.
3-9	9,200	64.0	5900	23.0	2100	10.5	870	2.5	230	0		Coryza.
3-15	5,200	54.0	2800	34.0	1800	8.5	440	3.0	110	0.5	30	
3-16	5,900	52.0	3100	38.0	2200	8.0	470	2.0	120	0		
3-19	6,300	50.0	3200	37.0	2300	10.0	630	2.0	130	1.0	60	
3-20	6,900	48.0	3300	41.0	2800	8.0	550	2.5	140	0.5	30	Coryza.

3. Mr. R., aged thirty-eight years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7,000	50.0	3500	39.0	2800	9.0	640	1.0	70	0		
1-13	8,500	56.0	4700	35.5	3000	7.0	600	1.0	80	0.5	40	
1-20	10,800	58.5	6300	31.0	3300	9.0	970	0.5	50	0		Extra heavy work and long hours in preparation for annual convention.
1-27	11,800	49.0	5800	41.0	4800	9.0	1060	0.5	60	0.5	60	
2-3	9,400	59.0	5500	34.0	3200	6.0	560	0.5	50	0.5	50	
2-10	8,900	56.0	5000	34.0	3000	9.0	800	1.0	90	0		
2-17	9,000	56.0	5000	35.0	3100	8.0	720	0.5	40	0.5	40	
2-24	5,400	51.0	2700	39.0	2100	9.0	480	1.0	50	0		
3-2	8,200	58.0	4700	31.0	2500	10.0	820	1.0	80	0		
3-9	7,400	55.0	4000	33.0	2400	9.0	660	2.5	180	0.5	40	
3-15	6,200	44.0	2700	45.0	2800	9.0	560	1.0	60	1.0	60	
3-16	7,100	47.0	3300	43.0	3000	8.5	600	1.0	70	0.5	30	
3-17	6,600	41.0	2700	45.0	3000	12.0	790	1.5	100	0.5	30	
3-18	7,300	45.5	3300	44.0	3200	10.0	730	0.5	40	0		
3-20	6,600	55.0	3600	36.0	2400	5.5	360	3.0	190	0.5	30	

4. Mrs. S., aged thirty-one years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7300	52.0	3800	37.0	2700	10.0	730	0.5	40	0.5	40	
1-13	7100	54.0	3800	33.0	2400	9.0	640	3.0	210	0		
1-20	8600	59.0	5100	29.0	2500	9.0	780	1.5	130	1.5	130	
1-27	8600	57.0	4900	31.0	2600	10.0	860	1.5	130	0.5	40	
2-3	8200	68.0	5600	24.0	2000	6.0	490	1.5	120	0.5	40	
2-10	6300	59.0	3700	31.0	2000	7.0	440	2.0	130	1.0	60	
2-17	6900	53.5	3200	36.0	2100	8.0	470	2.0	120	0.5	30	
2-24	8100	61.0	4900	30.0	2400	7.5	610	1.0	80	0.5	40	
3-2	6200	59.0	3700	27.0	1700	11.0	680	2.0	120	1.0	60	
3-9	6200	56.0	3500	35.0	2200	8.0	500	1.0	60	0		
3-15	6300	58.0	3700	33.0	2100	7.0	440	1.0	60	1.0	60	
3-16	6000	58.0	3500	32.0	1900	8.0	480	1.0	60	1.0	60	
3-17	7300	60.0	4400	32.0	2300	6.5	480	1.0	70	0.5	40	
3-19	9500	61.5	5800	30.0	2800	7.0	660	1.0	90	0.5	50	
3-20	6700	62.0	4200	30.0	2000	6.5	440	1.0	70	0.5	40	Tired.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8,700	66.0	5700	25.0	2200	8.0	700	1.0	90	0		Coryza for 2 days. Coryza.
1-13	10,000	52.0	5200	38.0	3800	8.0	800	1.5	150	0.5	50	
1-20	8,800	61.5	5400	27.0	2400	9.0	790	2.0	180	0.5	40	
1-27	8,500	58.0	4900	31.0	2700	9.0	770	2.5	220	0.5	40	
2-3	8,900	65.0	5700	24.5	2300	9.0	800	1.0	90	0.5	40	
2-10	9,600	63.0	6000	22.5	2200	12.0	1150	2.0	190	0.5	50	
2-17	8,200	62.0	5100	28.0	2300	8.0	660	1.5	120	0.5	40	
2-24	9,700	60.0	5800	32.0	3100	6.0	580	2.0	190	0		
3-2	7,600	54.0	4100	35.0	2700	9.0	680	2.0	150	0		
3-9	7,200	60.0	4300	32.0	2300	6.0	430	2.0	140	0		
3-15	9,700	56.0	5400	30.0	2900	9.5	920	4.0	390	0.5	50	Count taken at 11.15 A.M.
3-16	8,500	61.0	5200	29.0	2400	9.0	760	1.0	80	0		Mild "grippe." Up all night on ob-stetric case; tired.
3-17	7,200	61.5	4400	28.0	2000	8.0	570	2.0	140	0.5	40	
3-19	7,400	59.0	4400	31.0	2300	5.5	410	3.5	260	1.0	70	
3-20	11,000	63.0	6900	25.5	2800	9.0	990	2.0	220	0.5	60	

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8,000	55.0	4400	35.0	2800	7.0	560	2.0	160	0.5	40	Coryza. Not fully recovered from attack of "grippe."
1-20	6,600	55.5	3700	35.0	2300	8.0	530	1.0	70	0.5	30	
1-27	9,000	58.0	5200	32.0	2900	7.0	630	1.5	130	0.5	40	
2-10	11,800	67.0	7900	24.0	2800	6.0	710	3.0	350	0	..	
2-17	9,300	61.0	5700	27.0	2500	7.0	650	4.0	370	1.0	90	
2-24	8,700	56.5	4900	35.0	3000	6.0	520	2.0	170	0.5	40	
3-2	8,100	54.0	4400	38.0	3100	5.0	410	2.5	200	0.5	40	
3-9	8,900	58.0	5200	34.0	3000	4.0	350	3.0	260	1.0	90	
3-15	9,000	58.5	5300	34.0	3000	4.0	360	8.0	270	0.5	40	
3-16	8,400	56.0	4700	37.0	3100	4.5	380	2.0	170	0.5	40	
3-17	9,200	59.0	5400	32.0	2900	6.0	550	2.5	230	0.5	40	Mild indigestion. Mild indigestion..
3-19	9,000	60.0	5400	28.0	2600	6.0	540	4.5	410	1.5	130	
3-20	10,900	62.5	6800	31.0	3400	6.0	650	0.5	50	0	..	

[illegible]

8. Dr. B., male, aged thirty-five years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7,300	67.0	4,900	24.0	1700	7.0	510	1.5	110	0.5	40	Coryza. Coryza. Count taken at 11.45 A.M. Bad omelette for supper; some cramps; 3 loose bowel movements; felt O. K. when count was taken. But little rest past 24 hrs.; very ill patient.
1-13	8,000	65.5	5,200	26.0	2100	7.0	560	1.5	120	0	..	
1-20	8,400	67.0	5,700	24.0	2000	7.5	630	1.0	80	0.5	40	
1-27	10,400	66.5	6,900	24.0	2500	7.0	730	2.0	210	0.5	50	
2-3	7,400	66.0	4,900	24.0	1800	8.0	590	1.5	110	0.5	40	
2-10	9,000	69.0	6,200	21.0	1900	8.0	720	2.0	180	0	..	
2-17	7,600	60.0	4,600	30.0	2300	7.0	530	2.5	190	0.5	40	
2-24	7,500	67.0	5,000	25.5	1900	6.0	450	1.0	70	0.5	40	
3-2	8,000	64.0	5,100	25.0	2000	8.0	640	3.0	240	0	..	
3-9	12,600	82.0	10,400	13.0	1600	5.0	630	0	..	0	..	
3-15	8,500	58.0	4,900	29.0	2400	11.0	930	1.0	80	1.0	80	
3-16	12,000	69.0	8,300	21.0	2500	7.0	840	3.0	360	0	..	
3-17	7,600	64.0	4,900	27.0	2000	8.0	610	1.0	80	0	..	
3-19	8,100	71.0	5,700	21.0	1700	6.0	480	2.0	160	0	..	
3-20	9,800	72.0	7,000	21.0	2000	5.0	490	1.5	150	0.5	50	

9. Mrs. C., aged thirty-eight years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7500	59.0	4400	31.0	2300	8.0	600	1.5	110	0.5	40	Menses.
1-13	8000	65.0	5200	27.0	2200	6.0	480	1.0	80	1.0	80	
1-20	9000	65.0	5800	27.0	2400	6.0	450	1.5	130	0.5	40	
1-27	6000	63.0	3800	27.0	1600	7.0	420	1.5	90	0.5	30	
2-3	7000	61.5	4300	30.0	2100	7.0	490	1.0	70	0.5	30	
2-10	7000	66.0	4600	24.0	1700	8.0	560	1.5	100	0.5	30	Menses.
2-17	6700	62.5	4200	28.0	1900	8.0	540	1.5	100	0	0	
2-24	7300	66.0	4800	25.0	1800	8.0	580	1.0	70	0	0	
3-2	9000	61.0	5500	31.0	2800	4.0	360	4.0	360	0	0	
3-9	7800	61.0	4700	27.0	2100	6.0	470	5.5	430	0.5	40	
3-15	8200	61.0	5000	23.0	1900	12.0	980	3.0	240	1.0	80	Pityriasis about the same.
3-16	7000	63.5	4500	24.0	1700	11.0	770	1.5	100	0	0	Pityriasis much better.
3-17	6600	65.0	4300	24.0	1600	8.0	530	2.5	160	0.5	30	Menses.
3-19	8200	62.0	5100	27.0	2200	8.5	700	2.0	160	0.5	40	
3-20	Absent; vacation.											

10. Mrs. L., aged thirty-six years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7,200	45.0	3200	43.5	3200	8.0	580	3.0	220	0.5	40	Menses. Turkish steam bath last night. Menses.
1-13	6,000	46.0	2800	43.0	2600	7.0	420	3.0	180	1.0	60	
1-20	9,600	66.0	6300	23.0	2200	7.0	670	3.0	290	1.0	100	
1-27	7,400	51.0	3800	38.0	2800	7.0	520	3.0	220	1.0	70	
2-3	10,800	51.0	5400	40.0	4300	6.0	650	2.0	220	1.0	110	
2-10	6,600	53.5	3500	36.0	2400	8.0	530	2.0	130	0.5	30	
2-17	8,000	57.0	4600	34.0	2700	6.5	520	2.0	160	0.5	40	
2-24	7,700	48.0	3700	38.0	3000	9.0	690	4.5	340	0.5	40	
3-2	6,700	49.0	3300	42.0	2900	7.0	470	1.0	70	1.0	70	
3-9	7,800	63.5	5000	29.0	2300	6.0	470	1.5	120	0	..	
3-15	6,100	44.0	2700	46.0	2800	6.0	360	3.0	180	1.0	60	
3-16	6,700	55.0	3700	35.0	2300	7.0	470	2.0	130	1.0	70	
3-17	8,200	49.0	4000	41.0	3300	7.0	570	2.0	160	1.0	80	
3-19	6,400	52.0	3300	39.0	2500	4.0	260	4.0	250	1.0	60	
3-20	6,600	50.5	3300	39.0	2600	9.0	590	1.5	100	0	..	

11. Miss H., aged twenty-four years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	11,300	53.0	6000	34.0	3800	12.0	1360	1.0	110	0	..	Menses.
1-13	8,200	49.0	4000	39.0	3200	10.0	820	1.5	120	0.5	40	
1-20	13,100	69.0	7900	29.0	3800	8.0	1050	2.0	260	1.0	130	
1-27	12,300	60.0	6800	32.0	3600	6.0	680	1.5	170	0.5	60	
2-3	7,700	56.0	4300	34.0	2600	8.0	610	2.0	150	0	..	Menses; by request had 2 good nights of rest and quiet at home before count. Same routine as requested above.
2-10	7,700	55.0	4200	36.0	2700	7.0	540	0.5	40	1.5	110	
2-17	11,200	62.5	7000	28.0	3100	8.0	900	1.5	130	0	..	
2-24	9,000	63.0	5700	25.0	2200	9.0	810	2.0	180	0	..	
3-2	9,800	55.0	5400	34.0	3300	8.5	830	1.5	150	1.0	100	Menses.
3-9	11,200	52.0	6800	39.0	4400	7.0	780	1.5	170	0.5	60	
3-15	9,200	60.5	5500	31.0	2800	6.0	550	2.0	180	0.5	40	Feels unusually tired.
3-16	12,000	57.0	6800	33.0	3900	9.0	1080	1.0	120	0	..	
3-17	11,000	57.0	6300	35.0	3800	6.0	660	1.5	160	0.5	50	
3-19	10,200	55.0	5600	35.0	3500	8.5	870	1.5	150	0	..	
3-20	9,800	53.0	5200	36.0	3500	8.5	830	2.0	200	0.5	50	

GROUP II.—(ALL COUNTS BETWEEN 2.30 AND 3.15 P.M.).*

12. Dr. L., male, aged forty years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8,400	66.0	5500	25.0	2100	7.0	590	1.5	130	0.5	40	Sore throat early in week. Abscessing tooth.
1-13	11,800	69.0	8100	25.0	3000	5.0	590	1.0	120	0	..	
1-20	8,700	65.0	5700	24.0	2100	8.0	700	3.0	260	0	..	
1-27	10,300	63.0	6500	29.0	3000	3.5	360	4.0	410	0.5	50	
2-3	8,500	58.0	4900	33.0	2800	6.0	510	2.5	220	0.5	40	
2-10	10,500	66.0	6900	25.0	2600	6.5	680	1.5	160	1.0	100	
2-17	9,600	65.0	6200	26.0	2500	6.0	580	2.5	240	0.5	50	
2-24	8,800	71.0	6200	24.0	2100	4.0	350	1.0	90	0	..	
3-2	8,200	63.0	5200	28.0	2300	6.0	490	3.0	250	0	..	
3-9	8,700	58.0	4900	33.0	2900	6.0	520	3.0	260	0	..	
3-15	10,800	65.5	7100	26.0	2800	6.0	650	2.0	220	0.5	100	Unusually tired.
3-16	11,700	57.5	7300	35.0	4500	5.5	700	1.5	190	0.5	60	
3-19	12,500	71.0	8900	22.0	2800	4.0	500	3.0	380	0	..	

13. Dr. H., male, aged thirty-three years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remark.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8,700	62.0	5400	27.0	2400	6.0	520	3.0	260	2.0	190	Laryngitis for 24 hrs., voice husky.
1-13	9,600	63.0	6100	29.0	2800	6.0	580	1.5	140	0.5	50	
1-20	7,900	55.0	4400	29.0	2300	10.0	790	3.5	280	2.5	190	
1-27	10,200	57.0	5800	30.0	3100	7.0	710	5.0	510	1.0	100	
2-3	7,400	51.0	3800	37.0	2800	6.0	450	4.5	340	0.5	40	
2-10	7,800	57.0	4500	31.0	2600	7.0	550	4.5	350	0.5	40	
2-17	9,000	63.0	5700	28.0	2500	5.0	450	3.5	320	0.5	40	
2-24	9,600	52.0	5000	32.0	3100	10.0	960	4.0	380	2.0	190	
3-2	11,000	62.0	6800	24.0	2700	9.0	990	4.0	440	1.0	110	
3-10	9,100	52.0	5200	28.0	2600	10.0	910	3.0	270	2.0	180	
3-15	11,200	57.5	6400	33.0	3700	6.0	680	2.5	280	0.5	60	
3-16	7,600	56.0	4300	33.0	2500	7.0	530	3.5	260	0.5	40	
3-20	7,100	59.0	4200	31.0	2200	6.0	430	4.0	280	0	..	

* The total cells in all of the charts are accurate to within 100 cells for the neutrophils and lymphocytes and within 10 cells for the other cell types.

GROUP III.—(FIRST 6 COUNTS 9.30 TO 10.15 AM.; REMAINDER OF COUNTS
2.30 TO 3.15 P.M.*

14. Mr. S., aged eighteen years.

Date.	Total.	Polymorpho- nuclears.		Leukocytes.		Mono- nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	6,700	61.0	4100	27.0	1800	2.0	600	2.0	140	1.0	70	
1-13	6,200	47.0	2900	40.0	2500	10.0	620	3.0	180	0		
1-20	7,700	54.5	4200	35.0	2700	9.0	690	1.5	120	0		
1-27	6,300	42.5	2700	36.5	2300	16.5	1040	3.5	220	1.0	60	
2-3	6,400	53.0	3400	36.0	2300	8.0	510	2.5	160	0.5	30	
2-10	7,900	56.5	4500	30.0	2400	11.0	870	2.0	160	0.5	40	
2-17	6,000	61.0	3600	30.0	1800	8.0	480	0.5	30	0.5	30	
P.M.												
2-24	8,400	63.0	5300	25.0	2100	7.0	590	4.0	340	1.0	80	Coryza.
3-2	7,400	63.0	4600	26.0	1900	8.0	590	2.0	150	1.0	70	
3-9	5,700	51.0	2900	35.0	2000	11.0	630	3.0	170	0		Coryza last 2 days.
3-15	6,400	52.0	3300	40.5	2600	5.0	820	2.0	130	0.5	60	
3-16	6,500	55.0	3600	35.0	2300	8.0	520	2.5	160	0.5	60	
3-19	11,400	78.0	8900	14.0	1600	6.5	740	1.5	170	0		All-night party Sat. night; to bed 2 A.M. Sun. night; feels "all in."
3-20	11,400	72.0	8200	18.0	2000	9.0	1010	1.0	120	0		Feels much better after 10 hrs. sleep.

15. Miss W., aged thirty-four years.

Date.	Total.	Polymorpho- nuclears.		Leukocytes.		Mono- nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8700	64.0	5600	25.0	2200	6.0	520	4.0	350	1.0	90	
1-13	6300	53.0	3300	34.0	2100	9.0	570	3.5	320	0.5	30	
1-20	7800	57.0	4400	33.0	2600	6.5	510	4.0	310	0.5	40	
1-27	8400	59.0	5000	31.0	2600	7.5	540	1.5	130	1.0	40	Ac. coryza and laryn- gitis 14" to 16"; temp. 102; feels al- right now.
2-3	7600	55.0	4200	33.0	2500	8.0	610	4.0	300	0		
2-10	8100	56.0	4500	33.0	2700	7.0	570	4.0	320	0		Menses.
2-17	7500	51.0	3900	41.0	3100	5.0	380	3.0	230	0		
P.M.												
2-24	8800	54.0	4700	35.0	3100	8.5	750	2.5	220	0		
3-2	8500	57.0	4800	33.0	2800	6.5	550	3.0	250	0.5	40	
3-9	7300	58.0	4200	33.0	2400	6.0	440	2.5	180	0.5	40	Coryza.
3-15	7800	52.5	4100	35.0	2700	8.0	620	4.0	310	0.5	40	
3-16	8500	53.0	4600	38.0	3200	6.0	510	2.5	210	0.5	40	
3-19	9800	52.0	5100	39.0	3800	8.0	780	1.0	100	0		
3-20	7300	53.0	3900	38.0	2800	6.0	440	3.0	220	0		Hard manual labor, Sat. P.M. and Sun.

16. Miss E., aged twenty-five years.

Date.	Total.	Polymorpho- nuclears.		Leukocytes.		Mono- nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	7900	60.0	4700	39.0	2400	5.0	400	4.5	360	0.5	40	
1-13	9600	58.0	5600	32.0	3100	7.0	670	3.0	290	0		
1-20	7700	55.0	4200	30.0	2300	9.0	690	4.5	350	0.5	40	
1-27	8400	56.0	4700	34.0	2800	7.0	590	2.5	210	0.5	40	
2-3	8800	50.0	4900	32.0	2800	7.0	620	4.5	400	0.5	40	
2-10	6300	55.0	3500	35.0	2200	5.0	320	4.0	250	1.0	60	
2-17	8700	56.0	4800	28.0	2400	9.0	780	6.5	570	0.5	40	
P.M.												
2-24	7800	60.0	4700	27.0	2100	10.0	780	2.5	200	0.5	40	Menses.
3-2	8500	54.0	4600	34.0	2900	6.0	510	5.5	470	0.5	40	
3-9	7900	57.0	4500	31.0	2400	7.0	550	4.5	360	0.5	40	
3-15	7800	62.0	4800	25.0	2000	9.0	700	3.5	280	0.5	40	
3-16	8100	57.0	4600	30.0	2400	8.0	650	5.0	410	0		
3-19	9600	55.0	5300	35.0	3300	5.0	480	4.0	390	1.0	100	
3-20	7400	53.0	3900	34.0	2500	10.0	740	3.0	220	0		

17. Mr. H., aged seventeen years.

Date.	Total.	Polymorpho-nuclears.		Leukocytes.		Mono-nuclears.		Eosinophils.		Basophils.		Remarks.
		Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	Per cent.	Absol. No.	
1-6	8,100	47.0	3800	40.0	3200	6.0	480	6.0	480	1.0	80	
1-13	8,400	52.0	4400	37.0	3100	5.0	420	6.0	500	0		
1-20	10,000	45.0	4500	40.0	4000	9.0	900	6.0	600	0		
1-27	8,700	47.5	4200	38.0	3300	9.0	780	5.0	430	0.5	40	
2-3	7,100	51.5	3700	36.0	2500	9.0	640	3.0	210	0.5	40	Coryza.
2-10	7,800	51.0	4000	36.5	2800	9.0	700	3.0	230	0.5	40	Coryza.
2-17	8,600	63.0	5400	28.0	2400	5.0	430	3.5	300	0.5	40	
P.M.												
2-24	7,000	52.0	3600	36.0	2500	7.0	490	5.0	350	0		Coryza.
3-2	8,600	57.0	4900	35.0	3000	5.0	430	2.5	210	0.5	40	
3-9	8,300	46.0	3800	43.0	3500	7.0	580	4.0	430	0		Coryza.
3-15	7,400	51.5	3800	38.0	2800	8.0	590	2.0	150	0.5	40	Mild laryngitis.
3-16	8,100	48.0	3900	40.0	3200	6.0	480	5.0	400	1.0	80	
3-19	8,400	61.0	5100	33.0	2800	4.0	330	1.5	130	0.5	40	
3-20	6,900	41.0	2800	46.0	3100	8.0	550	5.0	340	0		

* The total cells in all of the charts are accurate to within 100 cells for the neutrophils and lymphocytes and within 10 cells for the other cell types.

Epicrisis. Upon analysis the data given above show many points of interest. No individual had a constant leukocyte count, either totally or differentially. Some individuals did not vary over 3000 (Mrs. C.) in their total counts, while others varied over 8000 (Dr. S.). In the differential counts one person did not vary over 7 per cent (Miss E.), while another varied over 30 per cent (Mr. S.). Because of these variations, it seemed of value to establish the *mode*, rather than the average, of the whole group. Chart I gives the graphs representing the total and the differential counts.

With regard to the total counts, it is noted that the largest number of counts were between 7000 and 8000. There were 172 counts between 6000 and 9000, with 12 counts below 6000, and 57 above 9000. This shows that, in spite of the variations, one may consider, as is usually done, that a total count between 6000 and 9000 is the usual normal, while counts above or below this are unusual and may be considered abnormal.

The neutrophil graph shows the largest number of counts between 55 and 59 per cent. There were 167 counts between 50 and 64 per cent, while below 50 per cent there were 39 counts, and above 64 per cent there were 35 counts. One may then consider that it is abnormal to have the neutrophils below 50 or above 64 per cent.

With regard to the lymphocytes, there were 183 counts between 25 and 39 per cent, with the largest number of counts between 30 and 34 per cent. There were about an equal number of counts below 25 and above 39 per cent. It would appear, then, that a lymphocyte percentage below 25 or above 39 may be considered abnormal.

The mononuclear leukocyte (the monocyte of Naegeli, and the endothelial leukocyte of Mallory) shows a plateau at 6 to 9 per

cent, with 176 counts within this range. There were a few more counts above 9 than below 6 per cent, but one may regard a percentage below 6 or above 9 as unusual and therefore abnormal.

Analysis of 241 Counts from 17 Individuals New York City, Jan. 6 to Mar. 20, 1928

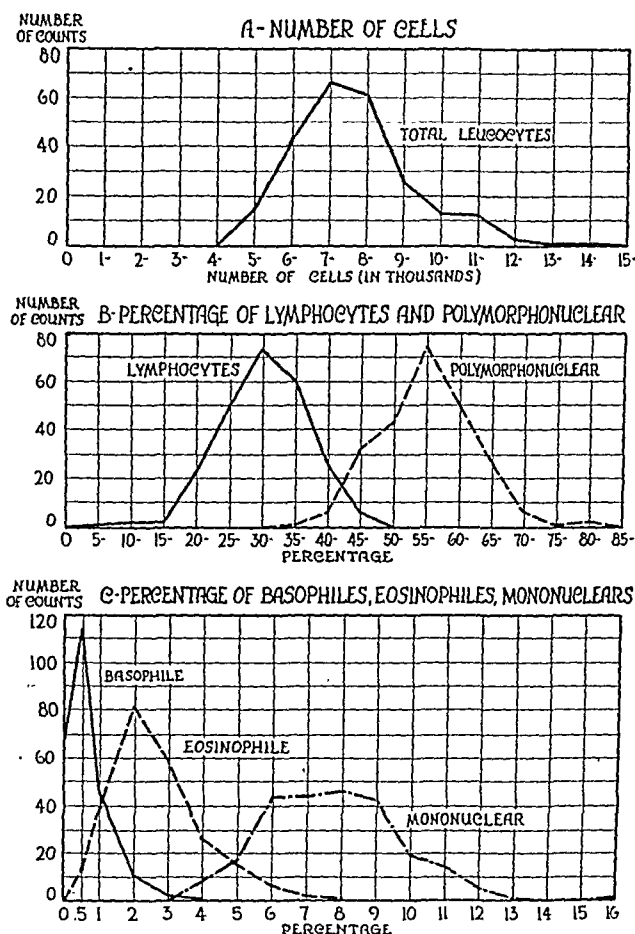


CHART I.

The normal eosinophil percentage appears to be between 1 and 3, and the basophil percentage 0.5 to 1. In the counting of 400 cells there were about one-third of the preparations which showed no basophils, while every count showed at least 0.5 per cent of eosinophils.

There does not appear to be any appreciable or constant variation between the morning and afternoon counts. It is recognized, of course, that these counts were taken at a relatively fixed time in the morning and in the afternoon. What variations might have occurred at other time intervals were not determined. The data here given show no evidence of a digestion leukocytosis. Just as

high counts were obtained in the morning as in the afternoon. (Compare Miss H. with all the counts in the morning, and Dr. L. with all the counts in the afternoon.)

An analysis of the counts taken during an ordinary "head cold" or a mild laryngitis shows no constant change. Most of the counts showed no marked change from the normal variation, while a few showed considerable variation. It may be stated that in this study no evidence was adduced to support the belief that ordinary mild infections of the upper respiratory tract have any influence on the leukocytic picture. The more severe infections may alter the leukocytic picture considerably. (Dr. S. last count.)

There does not appear to be any appreciable difference between the leukocyte content of the blood in the adult male and female. From the relatively small amount of data here presented the menses does not appear to affect the leukocytic picture in normal women.

A marked change can occur in the leukocytic picture of an individual without any evidence, clinical or otherwise, of an infection being present. Dr. B. developed a typical septic leukocytic picture after eating spoiled food. Mr. S. developed a typical septic leukocytic reaction after an all-night party which probably carried with it an abnormal demand upon his body tissues. Neither of these individuals had any of the signs or symptoms of an infectious process at the time the counts were taken.

Mrs. C. proved to be of interest in that she developed a very acute pityriasis of the greater portion of her body. The only appreciable alteration in her leukocytic picture was a rise in the eosinophils during the course of the disease.

Because of her relatively high leukocyte count Miss H. was asked to decrease her activities and to get at least eight hours of rest for two nights before the fifth and sixth counts. These counts were the lowest she had during the study. Whether the change in activity was the cause of the change in the leukocyte count is unknown, but it is at least suggestive.

Dr. S. showed the highest percentage of mononuclear leukocytes at the time he had an abscessed tooth. Mr. S. showed a mononuclear leukocyte count of 16.5 per cent without any clinical evidence of an infection being present at the time. Miss W. had the highest leukocyte count following strenuous physical exertion over the week-end, without there being any evidence of an infection. Dr. B. had the highest count twenty-four hours after an all-night vigil at an obstetric case.

There does not appear to be any greater variation in counts taken daily than in counts taken weekly in normal individuals. Where there occurred a greater fluctuation in the daily counts than was seen in the weekly counts an explanation for this change could be obtained. Whether the explanation offered really accounts for the alteration observed is, of course, a matter of conjecture.

Discussion. No originality is claimed for the differential classification of the leukocytes as used in this article. It is a grouping that has been extensively used in clinical practice for some years. The main purpose of the classification was to simplify as much as possible the number of cell types. It is admittedly incomplete, due largely to our incomplete knowledge of the exact origin, structure, developmental cycle and function of the different leukocyte types. Until such knowledge is completed, it seemed best to the author to adopt the simplest classification and technique possible.

There may be a difference of function or in age between the small and the large lymphocyte, but until such differences are fully established it would seem valueless to separate these cells into two groups.

By the use of a supravital technique differences in the finer structure of the monocyte and the clasmatoocyte may be demonstrated. Until it is well established that these cells are of different origin and have different functions it would seem best to group them together as mononuclear leukocytes. Because of the similarity of the cytoplasm, as seen in preparations made with Wright's stain, of the transitional leukocyte and the monocyte and clasmatoocyte, this cell has also been included in the group of mononuclear leukocytes.

There has been no attempt to classify the polymorphonuclear neutrophils according to the lobulations of the nucleus. Such a grouping gives valuable information relative to the demand for cells of this type. Such a study is not included in the present article which deals with the leukocyte content of the blood as a whole. Whether one chooses to use the method of Arneth,⁷ of von Schilling⁸ or of Pons and Krumbhaar⁹ is a matter of personal preference. The method of Pons and Krumbhaar, because of its simplicity, has an especial appeal to the routine worker.

It is doubtful if there exists an individual who has an absolutely stable leukocytic picture. If this be true then one must accept as a normal an individual in good health with no demonstrable variation from the average as far as physical or other findings are concerned. But even here an unrecognized pathologic condition may exist. One might postulate that if there were no damage to or alteration in tissue, either by infectious or noninfectious agents, there would be no need for leukocytes to exist in the circulating blood. Since such a condition is unobtainable with life as it exists today, one may again postulate that the leukocytes may be taken as an index of the status of the tissues in their complex environment. If that, in a sense, be true, then one could hardly expect to find any two average normal individuals with exactly the same leukocytic formula at the same time, unless those individuals were existing under exactly the same conditions. We believe, as Miller³ has stated, that the normal leukocytic picture of a community, and, if possible, of the individual, should be established if one is to get the proper interpretation of a leukocyte count in a pathologic process.

To illustrate, take two individuals, Mrs. C. and Miss W. Their

total counts were approximately the same when considered as a whole. Mrs. C. consistently had a neutrophil count above 60 per cent, while Miss W. had a neutrophil percentage below 60. In case Miss W. developed an acute appendicitis she might not run over 70 per cent neutrophils, whereas Mrs. C., under the same condition, might run over 80 per cent. Their total counts might, on the other hand, be similar. Or, again, take Dr. H., who had low total counts, and Miss H., who had high total counts. The differential percentage in each instance showed about the same range in variation. If Dr. H. developed acute appendicitis he might not have a total count over 10,000, which would be just as abnormal for him as it would be for Miss H. to have a total count of 15,000 to 20,000 under the same condition.

Our findings differ in certain aspects from the accepted textbook teaching. The total counts are the same. The eosinophils and basophils correspond. The percentage of neutrophils is lower, of lymphocytes and mononuclear leukocytes higher. Our findings agree in this respect with Bunting,¹ Stetson,² and others. They agree with Miller,³ except that we have found the mononuclear leukocytes higher.

The reports of Sabin⁴ and her co-workers, of Shaw,⁵ and of Fletcher and Mitchell⁶ have stressed the variation of the leukocyte counts in different periods during the day. Sabin, *et al.*,⁴ have concluded that there is practically an hourly rhythm and Shaw⁵ has found that there are diurnal tides in the leukocyte content of the blood. From these reports it would seem essential that blood counts be taken at relatively the same time of day if any reliance is to be placed on their significance.

It seemed to us that, since this variation occurs, it was fully as important to know how great a fluctuation might occur in a relatively short space of time. Consequently we took three normal individuals and did counts at three- and five-minute intervals for a period of one hour or two hours. The graphs shown in Charts II and III give the results of this study. To have constancy of technique the author took all of the blood samples and did all of the counts. The samples were "staggered" in such a manner that no knowledge was obtainable as to the sequence of events until the entire study of each individual was completed. We felt it desirable to rule out all personal factors.

The author had followed the leukocytic picture of these same individuals over a period of several months, the blood having been taken at the same time of day as the short interval counts were made. When a comparison between the record of several months was made with that of one or two hours it was found that these individuals showed just as great a variation in their counts in a period of one hour as they had shown over a period of several months.

It is interesting to note that the greatest fluctuation in the total counts would have been missed had the examinations been made at

longer intervals. And it would seem plausible that had intervals of shorter duration been used still other variations would have been found.

A critical analysis shows that the time interval of greatest fluctuation was different in each individual. In one case the time interval was twelve minutes, in another twenty minutes, and in the third the

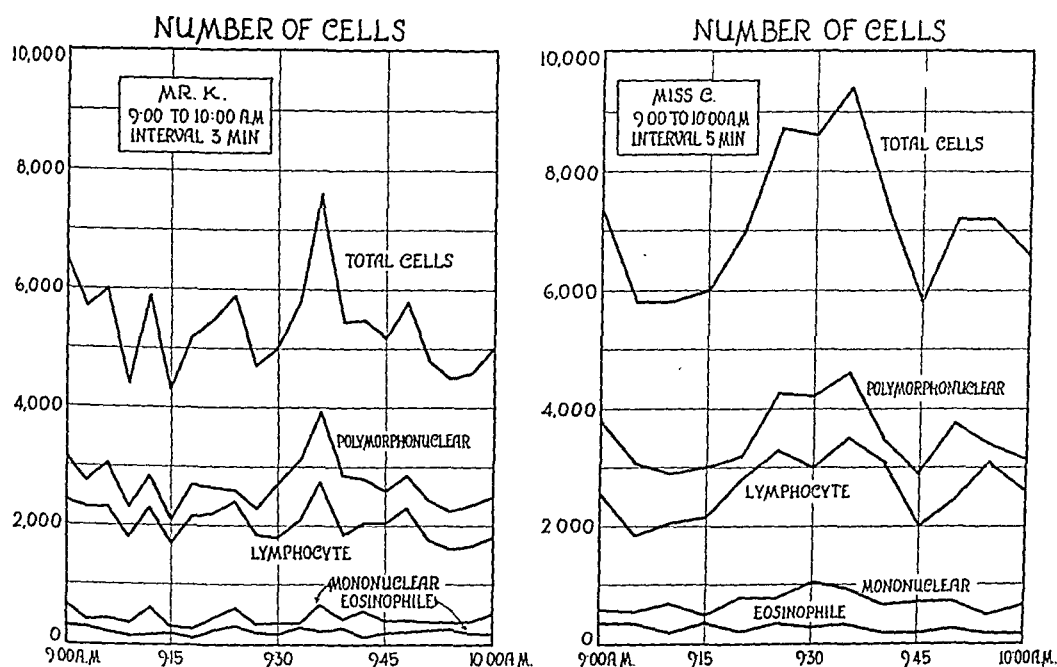


CHART II.

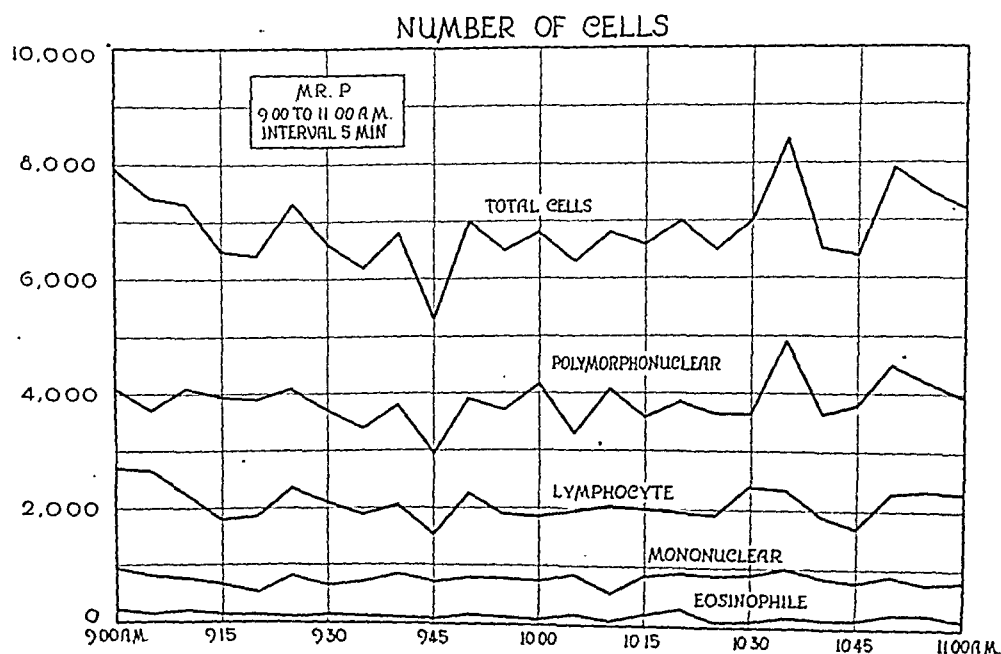


CHART III.

interval was fifty minutes. One grants that the fluctuation of a few hundred cells may be due to technical error, but a difference of over 2000 cells is due to some factor other than technical error. These observations do not appear to support the contention of Sabin, *et al.*⁴ that there is an hourly rhythm in the leukocyte curve, unless each individual has a different rhythm.

The report of Shaw relative to the diurnal tides of the leukocytes is of considerable interest in relation to the variation in a short period of time as observed by us. We have found as great a variation in the total counts within an hour as Shaw has shown in the diurnal tides. Our technique differed only in that he used but one pipette, whereas we were forced, because of the short time intervals, to use many pipettes. The same pipettes were used in each case studied, and the highest and lowest counts did not correspond to the same pipettes. So that it would seem that our results could not be explained by the use of different pipettes. From Shaw's report it appears that on the whole there were two periods of relatively long duration in which the counts were consistently higher than at other periods of the same duration. Since there occurs as great a fluctuation in the leukocyte counts within an hour as Shaw has shown in a twenty-four-hour period, one is led to wonder just how great a fluctuation might have been found had counts been taken at short intervals when the tide was at its height.

The differential counts showed less variation than the total cells. The greatest variation was 10 per cent, so that it would seem that the differential distribution of the cell types is more constant than are the total cells. A careful analysis shows, however, that there is a variation to a mild degree, so that at one time the increase or decrease was due largely to lymphocytes, at another time to neutrophils, and at a third time all cell types had contributed equally to the change.

This study shows that a normal individual, (studied under carefully standardized conditions) may show a variation of 50 per cent in the total count, and of 10 per cent in the differential count, IN LESS THAN HALF AN HOUR.

We have observed that the place from which the sample of blood is taken—finger or ear—has no influence on the differences observed in the counts, providing free-flowing blood is obtained. Four counts have been taken from a single puncture wound at three-minute intervals with less than a variation of 500 cells.

One might theorize at length as to the factors causing the variation that occurs in leukocyte counts. It would seem, however, that the simplest explanation is that there is an uneven distribution, up to a certain point, of the leukocytes, totally and differentially, in the circulating blood. For, after all, the body does not have a central collecting, mixing and distributing point for the leukocytes.

Conclusions. 1. A variation of 100 per cent in the total leukocyte count and 30 per cent in the differential may be found, even in a

carefully standardized study, in an average healthy individual in the course of weeks, without any clinical disease being manifest. This does not signify that there may not be an abnormal condition present in the body tissues. The least variation found in an individual during the period of this study was 30 per cent in the total leukocyte count and 7 per cent in the differential.

2. In the majority of instances mild infections of the upper respiratory tract caused no significant change in the normal leukocytic variation.

3. There is no constant difference between the leukocyte counts in adult males and females.

4. Menstruation does not appear to alter the leukocytic formula in normal women.

5. A septic leukocytic formula can develop in a normal individual without any clinical evidence of an infection being present. This reaction probably is caused by a non-infectious chemical alteration in the tissues.

6. Normal individuals can show as great a variation in their leukocyte counts in an hour as they show in daily or weekly counts taken over a considerable period of time.

7. It appears that the variation in the leukocyte count over a relatively short space of time is due to an uneven mixture, totally and differentially, of the leukocytes in the circulating blood. It does not appear to be rhythmic in nature, unless each individual has a different rhythm.

8. The greatest value of the leukocytic formula in pathologic alterations of the tissues can be obtained only when the normal leukocytic formula for a community and for an individual has previously been established. A normal person tends to maintain a leukocyte level, both totally and differentially, within certain limits under normal conditions.

9. The leukocyte MODE of the group of normal individuals reported in this study is as follows: Total count 6000 to 9000; differential count—neutrophils, 50 to 64 per cent; lymphocytes (large and small types), 25 to 39 per cent; mononuclear leukocytes (monocytes, endothelial leukocytes, transitional types), 6 to 9 per cent; eosinophils, 1 to 3 per cent; basophils, 0.5 to 1 per cent.

NOTE.—I desire to express my appreciation of the coöperation of Dr. A. S. Knight, Medical Director, and the members of the Medical Division of the Metropolitan Life Insurance Company in New York City and at Mt. McGregor, N. Y., in arranging for this study and in being willing to be the subjects for study.

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MARKED MONOCYTOSIS ACCOMPANIED BY A NEUTROPHILIC LEUKOPENIA FOLLOWING ANTISYPHILITIC TREATMENT.

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THE following case is reported as a type of reaction following antisyphilitic treatment in which the changes in the white blood cells were of great interest.

Case Report.—M. W., V. U. H. No. 5306, a colored female, aged twenty-four years, single, was admitted to the medical wards on October 26, 1927, with the complaint of chills, fever and sore throat. The past history was negative except for a sore throat four years previously. In July, 1927, she developed a skin rash but denied having had a primary lesion. She was first seen in the out-patient department on September 27, 1927, where a diagnosis of secondary syphilis was confirmed by the serum reaction, and treatment was instituted. On October 4, she was given 0.6 gm. of neoarsphenamin intravenously and 0.065 gm. of bichlorid of mercury intramuscularly and in addition saturated solution of potassium iodid, 20 drops to be taken orally three times a day, was begun. There was slight soreness at the site of the mercury injection but no further discomfort. On October 11, the injections of neoarsphenamin and mercury were repeated. The following night, October 12, the patient felt chilly and had one "hard chill," but on rising in the morning felt quite well and returned to work. On October 18, because of the reaction the preceding week, 0.6 gm. of sulpharsphenamin was given intramuscularly instead of the neoarsphenamin, while the mercury and iodides were continued as before. Immediately following this third treatment she felt faint. That evening she began feeling badly, a condition which became progressively worse until entry to the hospital, and there were associated fever (high fever, as the patient said), myalgia and repeated daily chills. On October 24, two days before entry and six days after her last treatment, her throat became sore, starting with sharp pains which increased until dysphagia was definite.

Examination on entry October 26, showed the patient to be alert, the skin hot, the temperature 101.6° F., pulse rate 120 per minute and respiratory rate 22 per minute. The skin showed a fading secondary syphilitic rash but no petechiæ, ecchymoses or jaundice. The eyelids were puffy. The epitrochlear, axillary, cervical and inguinal lymph nodes were moderately enlarged. The tonsils were swollen and red and there was a gray exudate on each. The tonsillar glands were enlarged and extremely tender but showed no signs of suppuration. The lungs were clear. The heart showed only a tachycardia. The liver and spleen were not felt. No vaginal or anal ulcers were seen. Neurologic examination was negative. Urine examination and phenolsulphonphthalein excretion were normal. A smear from the tonsils showed very few cells, none of these being of the polymorphonuclear group, and there was no predominating organism. Throat culture yielded a mixed flora with predominance of hemolytic streptococci. The blood culture was sterile, the Wassermann reaction positive. The blood studies on entry showed a moderate secondary anemia, the red blood count being 3,420,000 per c.mm. and the hemoglobin estimation (Sahli) was 75 per cent. The leukocyte count was 7950 per c.mm. (subsequently a

leukopenia was found) but a differential study showed a complete absence of the polymorphonuclear group. The smear did show, however, numerous platelets, many of which were quite large. More complete blood studies are given below in the discussion.

The patient's course was one of uneventful recovery and only symptomatic treatment was given. Sodium thiosulfate was withheld because of the steady improvement. The temperature reached the highest point, 103.6° F., the day of admission and returned to normal on the third day of hospitalization. Antisyphilitic treatment in the form of mercury inunctions and potassium iodid by mouth was resumed on November 2.

Examination on discharge from the hospital on November 5, showed a chronic tonsillitis, a faded secondary syphilitic rash, general glandular enlargement and a positive Wassermann. The out-patient record indicated no further symptoms following the treatment as outlined and the last blood counts have been normal.

Discussion. There are two points of especial interest in this case. The first is a reaction following antisyphilitic treatment characterized by symptoms of a generalized infection, a necrotic tonsillitis and a blood picture showing a mild secondary anemia, a leukopenia and an apparently complete suppression of the polymorphonuclear group of cells. The second is that while there is distinct evidence of systemic poisoning with a temporary disappearance from the circulating blood of one type of leukocyte, there is also evidence of stimulation of another type, the monocyte.

The general reaction and the clinical picture presented in this case classifies it as "agranulocytic angina." Schultz¹ states that there is a disease of unknown etiology, occurring in middle-aged females, fatal in its outcome and characterized by a febrile reaction, a necrotic tonsillitis and a leukopenia with suppression of the granulocytic series. To this, he gives the name agranulocytic angina. Schultz and Jacobowitz² make a further report based on 10 of their own cases and 13 from the literature and modify the first report by noting that it is not confined to females, that there is normal erythropoiesis, an absence of a hemorrhagic tendency and no thrombopenia. The review of Kastlin³ is complete and summarizes the findings in 43 cases, giving tables of the results. Case reports and shorter summaries may be found in the recent literature. The consensus of opinion at present is that this condition is not a disease entity as at first supposed, but that it is an expression of a reaction of unknown etiology. Feer⁴ suggests "sepsis agranulocytotica" as a more comprehensive term but this seems to add little to the better understanding of the condition.

Turning to the tissue response in the case reported, there are several interesting points for consideration and correlation with the findings in other reported cases and also with our knowledge of the effect of arsenic, benzene and the arsenobenzols on the leukopoietic "centers." At the same time a more important problem presents itself, namely, the type of the cellular response.

Table herewith gives the blood findings in the case under discussion and while it is self-explanatory certain points should be emphasized.

WILSON: MARKED MONOCYTOSIS

TOTAL AND DIFFERENTIAL BLOOD COUNTS.

Date.	Red blood count, per c.mm.	Hemo- globin, Sahli, per cent.	White blood count, per c.mm.	Polymorphonuclears.				Lympho- cytes small, large and in- termediate, per cent.	Mono- cytes, per cent.	Ratio of monocytes to lympho- cytes.	Myelo- cytes, per cent.	Platelets, per c.mm.	Clot- ting time, min.	Bleeding time, min.
				Neutrophils, per cent.			Baso- philes, per cent.							
				Neutro- philes, per cent.	Eosino- philes, per cent.									
Oct. 26, 1927	3,420,000	75	7950	0*	1.0	0	37 ?	62 ?	...	1.8	0	182,500	7	1.5
Oct. 27, 1927	3,695,000	65	4680	3.5	1.0	0	34.5	61.0	0.9	0.7	0			
Oct. 28, 1927	3,850,000	65	4760	16.0	1.0	0	41.5	39.0	0.9	0.4	1.5			
Oct. 29, 1927	3,850,000	65	4440	29.5	3.0	0	40.5	26.5	0.7	0.5	0.5			
Nov. 3, 1927	3,800,000	65	5040	51.0	2.0	0	34.0	12.0	0.4	0.2	3.0			
Nov. 4, 1927	3,270,000	63	4920	53.0	4.0	0	29.5	8.5	0.3	0	0			
Nov. 28, 1927	4,690,000	64	7840	60.0	2.0	0	22.5	7.5	0.3	0.3	0			
Jan. 19, 1928	4,400,000	75	7800	73.0	0.5	0	18.0	8.0	0.4	0.5	0.5			

* Wright's stain was used on their preparation. Subsequently the various leukocytes were differentiated by supravital staining.

* Wright's stain was used on their preparation. Subsequently the various leukocytes were differentiated by supravital staining.

It is evident that there was at first a moderate leukopenia followed by a gradual return of the white blood count to normal. The first differential study was made with Wright's stain. It showed no polymorphonuclear cells but did show the presence of a mononuclear cell which was difficult to classify into the customary groups. The first study by the supravital method revealed an almost complete suppression of the polymorphonuclear group, a total lymphocyte count slightly under normal and the number of monocytes considerably increased. These monocytes were definitely stimulated, being specifically of the type of monocytes seen in catarrhal jaundice and not of those seen in tuberculosis. Both types of monocytes have an increase in the vacuoles or bodies staining with neutral red. They differ, however, in that these vacuoles are much smaller and more numerous in tuberculosis (Cunningham, *et al.*⁵) while those in catarrhal jaundice are even larger than the normal. Subsequent differential studies showed a gradual return of the polymorphonuclear cells to the circulating blood with the appearance of myelocytes as well, the lymphocytes returned to a total number higher than normal while the monocytes fell practically parallel with the reappearance of the polymorphonuclear leukocytes, and at the same time qualitatively resumed their normal characteristics. The last observations indicated a normal blood picture.

The red blood count and hemoglobin determination showed a moderate secondary anemia without any notable qualitative changes in the cells and during the period of observations the total number of red cells returned to normal while the hemoglobin showed evidence of a "lag." In the first smear, the platelets were seen in abundant numbers, the total count on October 27, being 182,500. The clotting time, determined by the method described by Minot and Lee⁶ was seven minutes with a good retraction and a firm homogeneous clot formation. The bleeding time was one and a half minutes and the icteric index was five.

The point of particular interest is that, whatever the exciting cause, there was a remarkable stimulation qualitatively and quantitatively of the monocytes, a depression of the total leukocyte count, a complete suppression of the polymorphonuclear cells and practically no change in the number of lymphocytes. This picture is practically identical with the response to arsphenamin noted by Evans.⁷ Moore and Foley⁸ cite a case of arsphenamin poisoning in which there was a febrile reaction, an ulcerative stomatitis and a leukopenia with a relative increase in the large lymphocyte—transitional group of cells and depression of the polymorphonuclears. Case 7 of Krumbhaar's⁹ series of leukemoid blood pictures presents several interesting points of similarity.

The factor causing the blood reaction is not obvious. The possibilities are that it is the arsenic, the benzene or the combination of the two in the form of the arsenobenzols. By far the majority of the

reactions, following the use of the arsenobenzols, in which there is a change in the blood cells is a general bone-marrow aplasia. Dodd and Wilkinson¹⁰ summarize 24 cases of poisoning during the anti-syphilitic treatment giving the major blood findings. Their summary demonstrates that aplasia is common. In the report of the Arsphenamin Committee of the Medical Research Council¹¹ no definite evidence is given of a leukotoxic action following the administration of the arsphenamin group of drugs. The action of benzol as a leukotoxin has been worked out by Selling.¹² Clinical observations of benzene as an industrial poison are numerous and Weiskotten and his coworkers¹³ have published a series of papers on the action of benzol. In these studies a polymorphonuclear suppression was followed by a suppression of all the blood cells. Text-books of pharmacology do not speak of a leukotoxic action of the inorganic arsenic preparations despite the fact that Fowler's solution (*Liquor potassii arsenitis*) has been used for years in the treatment of anemia. The inorganic arsenic compounds are generally considered as stimulants to the red marrow and one would expect that any consistent action on the white blood cells would have been noted. In general, this has not been shown. However, 2 unpublished cases are recalled in which a leukopenia developed coincidentally with the use of Fowler's solution and there was also a suppression of the polymorphonuclears, but with a relative and not an absolute increase in the mononuclear cells. After discontinuing the drug, the blood counts and differential studies in these 2 cases returned to normal. A review of 28 cases of accidental arsenic poisoning by Lawson, Jackson and Cattanch¹⁴ shows in the surviving patients a leukopenia with a polymorphonuclear suppression and a relative increase in mononuclears at the end of five days with an evident tendency to establish a normal picture on the twelfth day. A few scattered reports indicate that a mild leukocytosis occurs in experiments on dogs in which arsenic was administered.

Many reports do not throw additional light on the underlying process of cell stimulation or cell depression because of the difficulty experienced in accurate cell differentiation. The white blood cells take on different characteristics under different stimuli and these changes are not easily recognized in fixed preparations. It would be of considerable interest to know what percentage of the mononuclear cells in the above-mentioned articles were lymphocytes and what percentage were monocytes. In the reported case, there is evidence that one type of white corpuscle may be suppressed, another type may be stimulated while a third type may be unaffected. This seems to indicate that, in adult life at least, the three types do not have a common parent cell.

Summary. The presented case shows an unusual, though not new, type of reaction to antisyphilitic treatment. Besides the interesting general reaction with septic tonsillitis there was a decided

action on the leukopoietic centers, in that a leukopenia was present with a depression of the polymorphonuclears and a stimulation of the monocytes. This type of case cannot with consistency be called agranulocytic angina in the sense that is usually attached to it. The causative factor is not evident inasmuch as arsenic, benzene and the arsenobenzol preparations occasionally all give rise to a similar picture, but the evidence seems to point to a poisoning by the benzene or arsenic rather than the conjugated arsenobenzol.

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ADENOMA OF THE ISLANDS OF LANGERHANS WITH ASSOCIATED HYPOGLYCEMIA.*

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AND

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ADENOMATA of the islands of Langerhans have been described, cases of hypoglycemia have been observed clinically and a malignant tumor of the islands of Langerhans with hypoglycemia has been reported, but our search of the literature to date has failed to show a single benign tumor of the islands of Langerhans associated

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with hypoglycemia proved by antemortem blood studies.* Because of this finding, we have been particularly interested in the following case:

Case Report.—A. J., a colored male, married, aged forty-one years, truck driver by occupation, was admitted to the Pennsylvania Hospital on December 21, 1927, with the chief complaint of attacks of loss of memory. During the summer and fall of 1927 he had complained of a very queer feeling which could not be localized or accurately described but which apparently occurred more commonly during the middle of the day. He was not a heavy eater and his meals were very irregular. He was particularly fond of hard candy and always carried some in his pockets, and at times when he felt queer he would stop his truck and get something to eat. On one occasion he came home from work feeling poorly, but after lunch, while his sister was about to notify his employer of his illness he felt so much improved that he insisted on returning to work.

His attacks which consisted essentially of loss of memory seemed to come on gradually and to last on an average of one and a half hours. Between attacks, he was apparently perfectly normal. During the last week in November, he was arrested three times for driving his truck past signs although previously he had always been a careful driver and had never been arrested. On the day of admission to the hospital, he suffered from one of these attacks and on being brought to the hospital was found to be in coma, but within an hour and a half he had regained consciousness and was anxious to go home.

Physical examination done on arrival at the ward was essentially negative. The temperature, pulse and respirations were normal. The routine urine and blood examinations were negative except for a leukocytosis of 13,700. A provisional diagnosis of epidemic encephalitis was made. Blood Wassermann and Kahn tests were later reported negative.

He had a supper consisting of house diet and was apparently comfortable. At 5 A.M. on December 22 he was found to be comatose. There were no definite signs of a cerebrospinal lesion. Examination of the spinal fluid was negative except for the finding of 20 mg. sugar per 100 cc. of spinal fluid. The Wassermann and Kahn and colloidal-gold tests on this fluid were negative. The blood-urea nitrogen was 17 mg., the creatinine 1.5 mg. but the sugar was only 40 mg. per 100 cc. On the next two subsequent days, the twenty-third and twenty-fourth, the blood-sugar determinations proved to be 42 and 38 mg. per 100 cc. respectively. His coma continued and a bronchopneumonia developed forty-eight hours before death. The only important findings were the persistent low blood-sugars in spite of the administration of glucose intravenously, by gavage and rectum. The amounts of glucose given, however, were relatively small as can be noted in the chart (Fig. 1). Death occurred on the afternoon of the twenty-fourth, seventy hours after admission.

The anatomic diagnosis made at autopsy, which was performed ten hours after death, was as follows: (a) Extensive bronchopneumonia of both lower and the right middle lobes. (b) Generalized arteriosclerosis. (c) Chronic myocarditis and nephritis due to arteriosclerosis (both moderate in extent). (d) Associated with cerebral arteriosclerosis, evidences of meningeal and cerebral irritation were definitely present, manifesting themselves in the form of slight perivascular round-cell accumulations showing that some form of mild cerebral irritation or inflammation was present, the nature of which we were not able to determine.

* In a personal communication from Dr. W. Thalheimer, of Milwaukee, Wis., we have recently had the opportunity of hearing of a case quite similar to the one we are reporting.

Of particular interest, however, was a lesion in the pancreas. This organ measured 17 by 4.5 by 1 cm., was homogeneous in consistency, and grayish in color. Projecting above the surface on the anterior aspect of the pancreas (Fig. 2) close to the superior border at the junction of the middle and distal thirds was a round, circumscribed nodule measuring 15 by 7 by 16 mm. It was soft in consistency and reddish-brown in color. Its surface was lobulated. On section, it was found to be vascular and to be surrounded by a delicate fibrous capsule. Gross examination of the rest of the gland was negative and the adrenals, liver and pituitary were also negative grossly and microscopically.

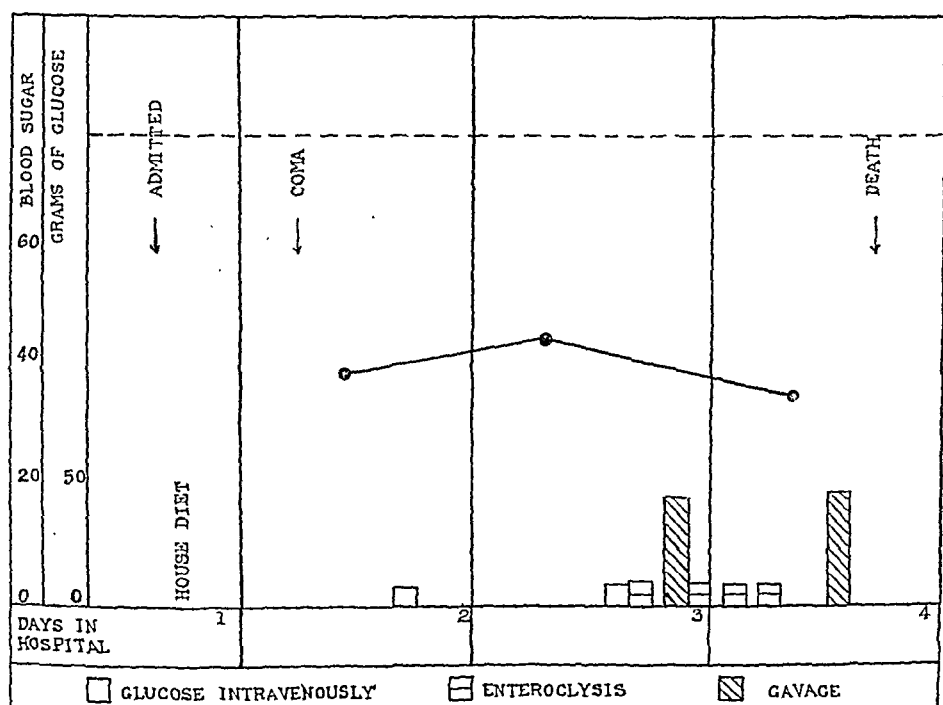


FIG. 1.—Diagram of the blood-sugar determinations in milligrams per 100 cc. The lower limit of normal blood-sugar values (80 mg.) is shown by the horizontal broken line at the top of the chart. The amount and manner of carbohydrate intake expressed as grams of glucose is also shown.

Microscopically, under low power, the tumor is partially separated from the surrounding pancreatic tissue by a fibrous tissue capsule (Fig. 3). In areas, however, both merge together gradually. Throughout the tumor the stroma in general is moderately developed although it is delicate in a few areas. The cells tend to have an alveolar arrangement surrounding blood spaces.

Under high power, the individual cell is polyhedral or cuboidal in shape with faintly granular eosin staining cytoplasm surrounding a small round nucleus rich in chromatin (Fig. 4). No zymogen granules are present and no mitotic figures seen. The growth is extremely vascular and the blood spaces do not appear to be lined with endothelium.

Associated with the adenoma there is a marked increase in size and in number of islands in the adjacent pancreatic tissue (Fig. 3). Bensley stains for island-cell differentiation and the biologic assay for the insulin content of both pancreas and adenoma (which was made through the kindness of Dr. D. A. Scott of the Connaught Laboratories of Toronto) failed because we had not fixed the tissues properly. From the morphologic appearance of the cells, however, we believe that they were of the beta type.

We are confronted, therefore, with a pancreatic lesion associated clinically with a diminution of the blood sugar and the question immediately arises as to whether or not we are dealing with an example of so-called "hyperinsulinism." In reviewing the literature on the question of hyperinsulinism, Harris¹ reports 5 cases of hypoglycemia in nondiabetic patients whose fasting blood sugars averaged 60, the lowest being 47 and the highest 67. The cardinal symptom in all these patients was weakness especially before the noon meal. Frequent feeding furnished great relief. Cammidge² reports a similar case in which the fasting blood sugar was 45. Attacks of giddiness were associated with this condition. Pemberton³ reports 2 similar cases. None of these cases were fatal while under observation and therefore the conclusions were drawn from clinical findings only. Most of these authors seem to agree that so-called hyperinsulinism is perhaps a disease entity, recognizing however, that the liver, adrenals, pituitary and thyroid gland may play some rôle.

A splendid review of the subject of adenomata of the islands of Langerhans has been made recently by Warren.⁴ Up to that time, only 20 cases had been reported in the literature. It is interesting to note that in 1 case only is there a history of diabetes and the lesions in the pancreas were mere subsidiary findings. The incidence is about equal in both sexes. The average age is fifty-seven years. Most of these cases were reported before the days of routine blood-sugar analysis. Hyperplasia of the surrounding islands associated with the tumor formation was reported in 5 cases. Cecil⁵ concludes that these tumors are part of a generalized hyperplasia of the islands while Warren states that "the lack of correlation with other lesions is rather against the interpretation of these tumors as hyperplastic islands."

Wilder⁶ has recently reported a case of carcinoma of the islands of Langerhans with metastases to the liver and lymph glands associated with hyperinsulinism and hypoglycemia. Alcoholic extracts of the tumor cells in the liver were found to be rich in insulin. He concludes, therefore, that the islet cells although they have undergone neoplastic change had retained the function of the parent cell.

Discussion. In our case, we have a lesion of the pancreas which may be regarded as an adenoma or as a greatly hypertrophied island. Its size, encapsulation and compression of surrounding pancreatic tissue favor the former view while the presence of many very large islands in the surrounding tissue suggest the latter condition. The question, as to whether hyperplasia of the islands is responsible for or secondary to the increased carbohydrate intake, is a debatable one. Hypertrophied islands in diabetics which from size alone might be considered adenomata have been described by Reitmann,⁷ Herxheimer⁸ and others. Gray⁹ reports a case of insular hypertrophy and hyperplasia associated with a low blood sugar in an infant of a markedly diabetic mother and suggests that



FIG. 2.—Sagittal section through the tail of the pancreas, showing the encapsulated tumor protruding from its anterior surface. Magnification $\times 1.6$.

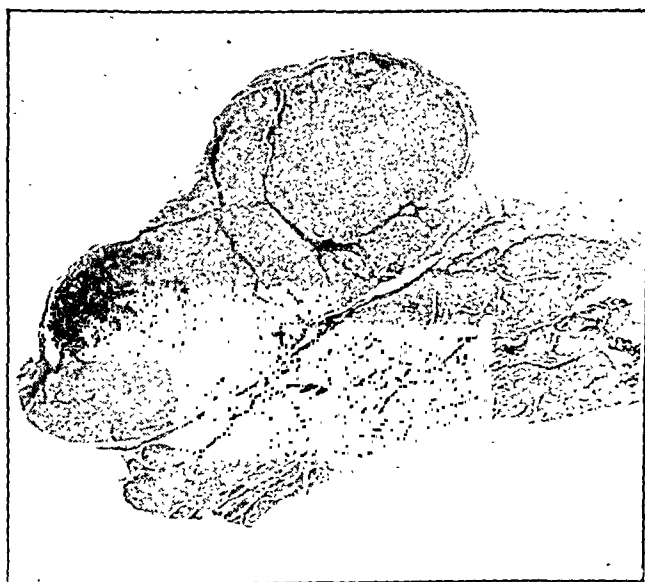


FIG. 3.—Low-power photomicrograph of the tumor and adjacent pancreatic tissue, in which the hyperplastic islets are seen.

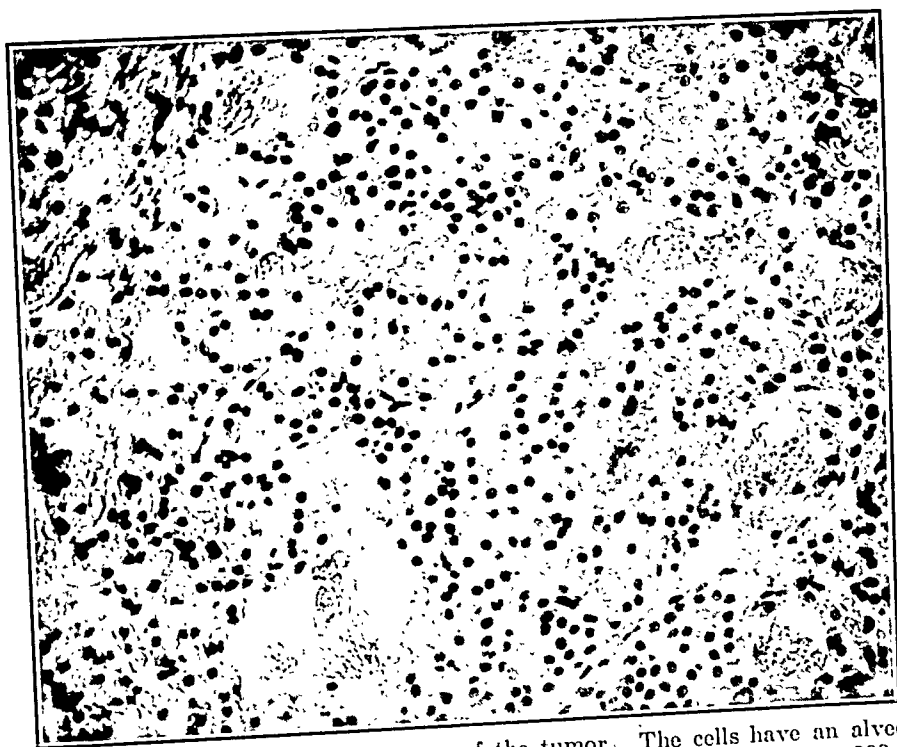


FIG. 4.—Photomicrograph, high-power, of the tumor. The cells have an alveolar arrangement surrounding blood spaces. Magnification approximately $\times 200$.

the maternal blood sugar may be the stimulus which called forth the increase in insular tissue. On the other hand, the increased carbohydrate intake may have been necessitated by the hyperinsulinism. There is little doubt but that this was the condition in Wilder's case and the peculiar clinical history in our case is more favorable to this opinion. Undoubtedly, hypertrophy and adenomata of the islands of Langerhans may occur without any demonstrable disturbances in carbohydrate metabolism. In the 20 cases reported by Warren the pancreatic lesions were subsidiary findings with no apparent clinical significance. Our case would strongly suggest, however, that under certain conditions there is definite relationship between the adenoma and a particular symptom complex. This may be due to the fact that the tumor cells have retained the function of the parent cells. In this connection, it is well to recall parallel conditions in other glands of internal secretion, for example, adenomata of the hypophysis and thyroid where tumor formation is associated with definite disease entities.

Summary. 1. A case is reported in which periodic attacks of hypoglycemia were associated with loss of memory or consciousness in a patient who was found at autopsy to have a lesion of the island cells.

2. The lesion consisted of a large circumscribed nodule (adenoma) which was found to be wholly composed of island cells and islands in the remainder of the pancreas were found to be markedly hypertrophied.

3. The significance of this relationship between hypoglycemia and hypertrophy or adenoma formation of the islands is alluded to and it would seem to add further evidence toward the creation of a new disease entity.

We wish to express our very sincere thanks to Dr. John R. Paul, Director of the Ayer Clinical Laboratory, who both in the preparation and study of the material and by his helpful criticism and interest in the paper has made this presentation possible.

We are also indebted to Dr. John T. Bauer and Miss Mary Naylor for their kindness and coöperation in doing the photography.

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THYROTOXICOSIS FROM THE INTERNIST'S STANDPOINT.*

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THE current literature on goiter is voluminous and one can scarcely hope to review it completely. New facts and theories are being constantly submitted. New discoveries may any day greatly modify and perhaps clarify our knowledge in this field, which at present is in a state of great confusion. We know very little of the pathologic physiology of hyperthyroidism and practically nothing of what excites the gland to this peculiar activity. Why will iodine convert a simple goiter into a toxic one and, in turn, tend to cause reversion of a toxic thyroid toward simple colloid goiter? Why is this relief at times temporary? Why does iodine fail to produce toxic symptoms, except in rare instances, in individuals with a normal gland? Why is hyperthyroidism, or in fact any form of goiter, so much more frequent in the female? Why do we occasionally see hyperthyroidism with a histologically normal gland? How can we explain the apparent presence in the same individual of both hypo- and hyperthyroidism? What about the group of patients with symptoms resembling mild hyperthyroidism with subnormal basal rates? Or another group, less common, with all the clinical manifestations of marked hyperthyroidism and normal rate, who, after a few weeks or months, develop a basal rate commensurate with the clinical findings? Why should a considerable number of hyperplastic hyperthyroids, after subtotal thyroidectomy, show a marked tendency to recur? Why is hyperthyroidism much more prevalent in regions where simple goiter prevails? What, if any, relation does the thymus bear to this disease? If we were only able to answer these questions it would illuminate many dark places and give us some understanding of this enigma.

The enlargement of the thyroid in infants, at puberty, and during pregnancy is considered physiologic—presumably a response to a greater need for its specific secretion. Strange to relate, the gland histologically in these cases bears a striking resemblance to the hyperplastic goiter of hyperthyroidism. Similar histologic changes are observed in dogs after lobectomy, and are referred to as compensatory hyperplasia. Although histologically closely resembling the gland of hyperthyroidism, the physiologic goiter does not give rise to toxic signs or symptoms. Some observers, however, believe that the instability of the nervous system at puberty is really a mild form of hyperthyroidism. Aschoff refers to some work done

* Read before the Chicago Society of Internal Medicine, May 28, 1928.

by Hellwig where he was able to demonstrate increased basal metabolic rate in this group of cases.

Iodin will, as a rule, prevent these physiologic hyperplasias. It will also prevent hyperplasia in dogs, following lobectomy, provided the amount of thyroid removed (according to Marine) does not exceed about two-thirds of the total gland substance. In both man and dog, after iodine, the hyperplasia disappears and the gland reverts to the colloid type which both biologically and anatomically is the nearest approach to normal that a previously hyperplastic thyroid may attain. During the hyperplasia, the flat or cuboidal epithelial cells lining the alveoli, hypertrophy—becoming columnar or cylindrical and at the same time increase in number, a true hyperplasia. The colloid is either greatly lessened or may entirely disappear from some alveoli. After iodine, there is a reversion to the normal cuboidal cell with reappearance of colloid.

Physiologic hyperplasia is wide spread and is not confined to goiterous districts. In goiterous regions, however, the response is more marked.

The amount of iodine required to prevent hyperplasia is exceedingly small. In Switzerland, the iodized salt which they find satisfactory contains 5 mg. of iodine per kilogram. They estimate that the average individual will consume about 3 kilograms of salt annually and he, therefore, receives about 15 mg. of the iodine. Iodized salt in this country contains 200 mg. of iodine per kilogram. This raises the amount consumed in a year to 600 mg. or 40 times that of Switzerland. It is estimated that the annual requirement of the thyroid under normal condition does not exceed 50 mg. It appears, therefore, that iodized salt in this country contains far too much iodine. The Swiss physicians claim that the amount of iodine we add to salt will convert many simple goiters into the toxic type, and there is a growing belief that this actually occurs in the United States.

Formerly, practically all the dogs used in the physiologic laboratories at the University of Chicago had goiter. Now, I am told by a member of this department that canine goiter has become rare, which he ascribes to the widespread use of iodized salt—the average dog living largely on table scraps.

With advancing years, the thyroid atrophies and may be reduced to one-half the normal size. Both epithelium and colloid are greatly lessened. This atrophy of age, however, must be taken into consideration in the surgery of the thyroid. We will be better able to determine whether subtotal thyroidectomy is a safe procedure when patients so treated have been followed to the three score years and ten.

Mobius' monograph on exophthalmic goiter, published in 1886, was the first clear exposition of this disease. Little has been added to the clinical syndrome as presented by him. No one has improved

on his definition of this disease—"Basedow's disease is an intoxication of the body due to abnormal activity of the thyroid."

The pathologic histology of the thyroid in hyperthyroidism has attracted much attention and it is quite generally accepted that there is not a single picture. Since we have outgrown, thanks largely to basal metabolism, the old classical triad of goiter, exophthalmos and tachycardia, we know that many of these patients have no material enlargement of the thyroid.

Two general types of gland may be recognized—the diffuse hyperplasia and the nodular or so-called adenomatous type. It is at present generally conceded that the adenomas do not arise from fetal rests; and, unlike these, may function much as normal thyroid tissue, having periods of hyperplasia followed by a resting stage. Aschoff believes adenomas arise from apparently normal thyroid tissue, especially that centrally located in the lobule. It is at present debatable whether the adenoma is a real tumor or merely a parenchymatous hyperplasia.

Some simple adenomas respond to iodine in the same manner as the hyperplastic thyroids. We know that a so-called toxic adenoma will respond quite as well to iodine as the exophthalmic type. De Quervain agrees with Aschoff that the adenoma may be capable of hypo- and hyperfunctioning just like the normal gland. In some cases they believe the hyperplasia is confined solely to the adenomas. More frequently, however, the adenoma is unchanged; the surrounding thyroid tissue alone being involved. In 16 cases of toxic adenoma, W. G. MacCallum¹ found only 1 in which the nodule showed the hyperplasia and infolding character of hyperthyroidism. In only 1 instance was the hyperplasia limited to the adenoma.

Recently W. F. Reinhoff and Dean Lewis² have studied the thyroid in 189 cases of so-called toxic adenoma. In 9 of these, the nodule resembled a true benign parenchymatous neoplasm, but in no instance did it participate in the hyperplasia which was present in the surrounding thyroid tissue. In 34 per cent, the nodules were due to colloid cysts. All of this group was found in long-standing cases, and they believe this change is due to overinvolution occurring during spontaneous remissions or following the use of iodine. These involuted nodules show hypertrophy and hyperplasia similar to that of the surrounding thyroid tissue. In the remaining 63 cases (58 per cent), the nodules were due to circumscribed hyperplasia of limited areas of the gland with intervening normal tissue. In these cases the hyperplasia was merely circumscribed rather than diffuse. All of this group showed a rather moderate degree of intoxication. If their findings are confirmed, the nodules found in toxic goiters may be true adenomas, overinvolved tissue, or circumscribed areas of hyperplasia. With the available evidence, it would appear misleading to continue to use

the term "toxic adenoma." It is more accurate to say "hyperthyroidism with nodular goiter" or still better "thyrotoxicosis with nodular goiter."

The histologic picture in the hyperplastic gland in hyperthyroidism resembles quite closely that of the physiologic hyperplasia of puberty—the chief difference is one of degree; the hyperplasia being much more marked in hyperthyroidism. The superficial vessels became dilated thus accounting for the bruit. The gland is firm and when cut presents a uniform red dry appearance—the latter being due to lessened colloid. Histologically, it differs from the normal in the great reduction in colloid. The acini appear small; some of them may be practically obliterated. The epithelial lining often buckles, leading to papillary projections into the acinus. The cells have been transformed from the normal flat type into high cuboidal, columnar or even cylindrical forms—a true hypertrophy. In addition, there is marked hyperplasia, due to formation of new epithelial cells. This hypertrophy and hyperplasia accounts at least in part for the constriction of the acini. In addition, islands of lymphoid cells may be seen. Similar lymphoid areas may be observed in the ordinary colloid goiter and cannot be considered a special characteristic of the gland in hyperthyroidism.

If we were able to eliminate the cases of Basedow's with histologically normal glands, it would simplify the problem very much. It is true that in many cases there are islands of hyperplasia, with intervening normal gland tissue. However, those who have studied this question carefully admit that we may have typical hyperthyroidism without evidence of epithelial hyperplasia. Aschoff says that we may have hyperplasia without Basedow's and Basedow's without hyperplasia. This would suggest that hyperplasia is not essential to hyperthyroidism. We should bear in mind, however, that an exceedingly small amount of hyperplastic tissue may be responsible for marked intoxication. Not infrequently following a subtotal thyroidectomy, when the symptoms fail to abate the very small amount of thyroid tissue attached to the posterior capsule (too small to be detected by palpation) may cause the same degree of intoxication as the entire gland. Dr. Phemister recently showed a patient where, after subtotal thyroidectomy, the basal rate remained high—about +50. Several months later, a second operation was performed in order to determine whether a portion of the thyroid may have been overlooked. Two small pieces of tissue, the size of a pea, were found in the region of the lower poles and the blood-vessel entering these nodules was ligated. The basal rate promptly dropped to normal and the patient returned to work for six weeks, when the basal rate rose to +70 with return of symptoms. If such a small amount of tissue may cause intoxication, it is possible that Basedow's with reported normal thyroid, may contain small areas of hyperplasia which have been overlooked.

There is extreme variation in the iodine content of the normal thyroid. Bauman, and Zeit,³ who first determined the iodine content of the thyroid, found the average amount to be about 6.6 mg. In the normal thyroid, however, variations were found from 1.7 to 27 mg.

Oswald determined the iodine in 119 normal glands in Switzerland with a variation of from 0.48 to 13.6 mg. He found the normal gland in Sweden did not differ in its iodine content from that of Switzerland—thus disproving the view held by some that the thyroid near the ocean contains more iodine. He examined 43 simple goiters in Switzerland; the iodine content varied from 11.7 to 26.9 mg. The colloid goiters had the largest amount; less in the parenchymatous type; and least in the adenomatous—while the total iodine was greater than in the normal the amount per gram of dried gland was less.

As a rule, the gland in hyperthyroidism contains relatively much less iodine than the simple colloid goiter, although the total iodine content may be greater than the normal gland. Marine states that the iodine content varies directly with the amount of colloid and inversely with the degree of hyperplasia. In other words, colloid is essential for the storage of iodine. Marine reports Basedow's thyroids with a higher percentage of iodine per gram of dried gland, than in colloid goiter. Oswald confirms this. We may conclude from this that deficient iodine in the gland is not an essential factor in hyperthyroidism.

There is considerable difference of opinion in regard to the iodine content of adenomas in hyperthyroidism. Marine believes the iodine content of the adenoma is less than in the surrounding tissue. De Quervain, on the other hand, states that he has seen adenomas with three times the amount of iodine present in the surrounding tissue.

The effect of administering iodine on the iodine content of the gland has been studied by Jansen and Robert.⁴ Without previous iodine, the average percentage of iodine expressed in milligrams in the fresh normal gland was 9.39; colloid goiter, 4.87; mild hyperthyroidism, 5.64; severe hyperthyroidism, 6.81—showing a relative iodine deficiency in hyperthyroidism as compared to the normal, but a slight increase in the total iodine content of the gland.

The normal gland after iodine shows a relatively great increase in iodine. The simple goiter took up iodine much less readily than the normal gland, although there was both a relative and absolute increase. The gland in hyperthyroidism behaved in much the same manner as in simple goiter—a moderate relative and absolute increase; the milder the degree of intoxication, the less the increase in iodine.

They also studied the iodine content of blood. Without previous administration of iodine in colloid goiter, the iodine content of the

blood was about 30 per cent of normal. In Basedow's, the blood iodine was increased three-fold over the normal. There was no relationship between the amount of iodine in the blood and the iodine content of the gland. This would suggest that the Basedow's thyroid is lacking in ability to store iodine or, as the writers believe, there is an excessive production of thyroid hormone.

The blood in simple colloid goiter, after iodine, contained a great increase in iodine—showing that excessive iodine in the blood *per se* was not responsible for the intoxication. Some individuals with simple goiter, both colloid and adenomatous, who after iodine became toxic did not show relative or absolute increase in the iodine content of the gland. In other cases, the relative and absolute iodine content of the gland was increased, but there was no change in blood iodine. Apparently, there is a qualitative factor in the secretion which may or may not be iodine in nature.

Reinhoff⁵ has studied the anatomic changes in the thyroid of Basedow's after iodine. A small piece of the gland was removed previous to the administration of iodine and compared with the sections at time of operation. After iodine, the gland became softer and somewhat smaller. The cut surface dripped with a glairy fluid which proved to be colloid. Cells showing mitotic figures disappeared. The hypertrophy and hyperplasia of the epithelial cells was lessened or in certain areas had entirely disappeared. The vascularity was less; some of the vessels were collapsed from pressure of colloid in the distended acini. This supports Marine's view that the action of iodine in hyperthyroidism is mechanical, interfering with the escape of the secretions into the circulation. In case the thyroid contained an adenoma, Reinhoff found it showed increase in the colloid.

Cattell,⁶ studied a series of the thyroids where the patient had preliminary iodine. In 88 per cent, the hyperplasia was much reduced judging from what is seen in the untreated thyroid. In 6.7 per cent he believed the hyperplasia was increased.

Giordano⁷ reports that in Basedow's patients who received iodine for one month, it was practically impossible to differentiate sections of the thyroid from a normal colloid gland.

No attempt will be made to discuss the changes in, or the relation of, the various ductless glands, except thymus, to hyperthyroidism. The very frequent presence of an enlarged thymus has raised the question of its possible relationship to hyperthyroidism. Warthin believes that hyperthyroidism only occurs in individuals with the so-called lymphatic constitution. A person, to develop this disease, must first have an enlarged thymus. He does not express an opinion in regard to the nature of this relationship.

Capelle⁸ reports enlarged thymus in 95 per cent of hyperthyroidism dying following operation. Furthermore, 82 per cent of those dying directly from the disease and 44 per cent dying from inter-

current disease had enlarged thymus. Marine considers the enlarged thymus as secondary to the hyperthyroidism; part of a systemic reaction.

Garre reports a cure after thymectomy; and in Roentgen ray therapy of Basedow's the thymus region is treated and may be one factor in the beneficial results.

The pathologic physiology of hyperthyroidism is still highly speculative. No attempt will be made to present all the various hypotheses. Krehl believes that individual predisposition is a very important factor—the nature of this he does not attempt to explain. In support of this view, he mentions the inability to produce hyperthyroidism in every individual with simple goiter with either iodine or powdered thyroid.

Aschoff has a similar theory except that he considers this individual susceptibility as due to a hypersensitiveness of the nervous system. This, he believes, rather than an increase or abnormal secretion is responsible for the symptoms. He calls attention to the ease with which hyperthyroidism can be excited with dried thyroid, in an individual who has been cured by partial thyroidectomy. He believes there is more than one active principle and that a disturbance of balance in the relative amount of these may play a rôle.

Oswald advances the theory that the primary disturbance lies in the epithelial cells of the thyroid. No explanation is given for this cellular disturbance. The function of the epithelium is to remove the iodine from the blood and convert it into iodoglobulin so that it may be stored in the colloid; somewhat similar to the glycogenic function of the liver. Only iodine in this form is biologically active. He believes the epithelial cell has lost its power to convert iodine into a form where it can be stored; the iodine, consequently, is rapidly excreted from the body. This might account for the high iodine content of the blood in hyperthyroidism. The lack of storage ability leads to iodine deficiency. The reserve iodoglobulin disappears and with it the colloid. The compensatory hyperplasia is a response to inadequate thyroid secretion. This theory makes a strong appeal.

De Quervain leans toward multiple rather than a single active substance. Whether iodine is an important ingredient in all of them, he believes is an open question. He refers to Kendall's experiment where he obtained different physiological results with a substance soluble in acid from that obtained with a substance soluble in alkalies. He calls attention to the disassociation of the symptoms in cretinism, which he considers speaks for more than a single action substance. Here the gland is not always atrophied and at times the histologic structure suggests we are dealing with an active secreting tissue. The cardinal symptoms of cretinism are skeletal changes, intellectual defects and deaf-mutism. He states that in

cretins who are dwarfed, the thyroid is atrophied, while in those without skeletal defects the thyroid is at least normal in size and there is usually an obvious goiter. The genitalia and growth of hair are defective in the dwarfed cretin and not in the one of normal stature. Any explanation of the pathologic physiology must take into consideration the very small amount of thyroid tissue required for intense intoxication. This, apparently, discounts the view that we are dealing with a pure hypersecretion.

There is considerable confusion and inaccuracy in the current use of the term hypothyroidism. A patient with clinical myxedema or cretinism may be said to have hypothyroidism. Every patient, however, with a subnormal basal rate does not suffer from hypothyroidism. Perhaps in the future a clinical syndrome may be discovered which will enable us to detect a milder degree of thyroid deficiency than our present clinical myxedema. At present, however, clinical myxedema should be accepted as the criterion of hypothyroidism. Basal metabolism alone does not enable us to make such a diagnosis. We have at present under observation a lassie of 13 summers, with a goiter and a basal rate of -24 . She is a normal alert individual. Another patient who about one and a half years ago had a subtotal thyroidectomy, now has a definite myxedema with a basal rate of -12 .

The diagnosis of hyperthyroidism is not by any means always an easy task. The very slight enlargement of the gland in many instances and the great frequency of simple goiter, complicates the diagnosis. Most puzzling is that small but definite group where the signs and symptoms antedate an increase in the basal rate. There is another type, observed in individuals later in life and especially in long standing hyperthyroidism, where tachycardia or fibrillation is present but with a basal rate only slightly above the normal limit. These patients respond to iodine and the cardiac symptoms disappear permanently after subtotal thyroidectomy. This group can be easily overlooked and diagnosed as chronic heart disease.

Patients with goiter and hypertension may show an increased basal rate in the absence of hyperthyroidism. Here the temporary use of iodine may be of great assistance in determining the cause of the increased basal rate.

Occasionally we see a patient where after careful study we are in doubt as to whether we are dealing with a functional nervous disturbance or hyperthyroidism. I believe it is unwise to settle this question by subtotal thyroidectomy. Such a patient can well be kept under observation for a few weeks with frequent determinations of the basal rate, until such a time as we are satisfied with the diagnosis.

A considerable number of iodine hyperthyroidisms, either the direct result of iodine prescribed by the physician or from the use of iodized salt, have been observed during the past two years. Many of these

will return to normal after merely withdrawing the iodine. One such patient with a basal rate of +54 per cent, within six months had a subnormal rate with disappearance of symptoms. If one is certain of the cause, I believe that these patients—unless suffering from intense intoxication—can be wisely kept under observation for at least two months before advising radical treatment.

The purely medical treatment with the purpose of effecting a cure can be quickly dismissed. It is safe to say that drug therapy does not cure, although patients so treated may temporarily regain their health due probably to the tendency of this disease to spontaneous remissions. There is at present a widespread practice of looking on iodine as a curative agent. It cannot be too strongly emphasized that its chief field of usefulness is limited to preparing a patient for operative measures. Digitalis, I believe, is not indicated except in auricular fibrillation and here it fails to act in as satisfactory a way as in fibrillation of other origin. The best cardiac treatment is rest in bed.

The futility of physical and mental rest in the hope of effecting a cure has recently been demonstrated by Kessel and Hyman.⁹

We must conclude that there are only two forms of treatment that offer great hope of benefit or cure—surgery and Roentgen ray. I cannot at all agree with those who believe or at least state that Roentgen ray is valueless. After an experience extending over ten years, I am convinced that Roentgen ray is a valuable form of therapy and is free from certain undesirable complications as laryngeal paralysis, tetany and myxedema. Since the use of iodine as a pre-operative treatment, and lessened operative mortality, one of the arguments in favor of Roentgen ray has been removed.

What the internist awaits is the presentation by someone of satisfactory evidence of the percentage of cures by these two methods. By evidence, is meant the following of a series of cases treated by either of these methods for a period of five years. This follow-up cannot be done by a questionnaire which, at best, is a crude and unscientific method of obtaining therapeutic information. This is especially true of goiter, as shown by the character of the reports in the very limited series in the literature.

To obtain actual information, the previous patient must be examined by a competent physician both from the standpoint of clinical manifestations and basal metabolism. Such a method of follow-up requires much time and perhaps considerable expenditure of money. When we consider the very large sums spent on research—often with very meager returns—a problem of this character which must yield valuable information, and is true research, merits financial support. This matter has been emphasized because in my experience the results from surgery have not been as brilliant as we would expect from reading the literature.

Very recently a report has been made and to the best of my knowl-

edge, the only one in the literature, which fulfills these requirements, except that the period of observation is too brief to arrive at final conclusions. This is from the Lahey Clinic in Boston (Smith, Clute, Steider¹⁰). One hundred consecutive patients, operated upon at least one year previously were examined every three to four months by a competent clinician and at the same time the basal rate was determined. One patient died three months after operation; 92 were reported as having complete relief from their hyperthyroidism; the remaining 7 were definitely improved—were capable of doing a large part of their daily tasks, but still presented evidence of intoxication. The average basal rate of this group was $+26.4$ per cent; the highest $+40$ per cent; the lowest $+7$ per cent. Of the group free from symptoms of hyperthyroidism, 19 had a basal rate of -10 or more; 15 of these showed definite evidence of clinical myxedema and were taking thyroid extract or thyroxin. Even with the greatest care in regulating the dosage, they were unable to bring these patients to a normal functioning ability. They all show evidence of lack of endurance—fatiguing very easily. With further moderate increase in thyroid extract, they would develop symptoms of hyperthyroidism. It is true they were in much better condition to earn a livelihood than before the operation. It will be interesting to see if this entire group is followed, we may say for five years, whether more of these patients will develop myxedema. The lesson drawn from this report is that a treatment that effects a very high percentage of cures brings in its train a relatively high percentage of myxedema. This careful report is impressive as it indicates that much is still to be desired in the surgical treatment of hyperthyroidism.

If by treatment with Roentgen ray an equal per cent of recoveries can be shown, with lessened frequency of myxedema, then Roentgen ray would be the preferred method of treatment. For the purpose of comparison, we await with interest a report where equal care has been given to the follow-up Roentgen ray therapy.

During the many years in which a less radical removal was practiced, the permanent cures were probably in the neighborhood of 70 per cent. These results are comparable with what is accomplished with Roentgen ray. Postoperative myxedema was rare, at least in this country, and I have never seen a myxedema following Roentgen ray therapy, although they do occur. With the more radical procedures, the number of cures has reached approximately 90 per cent, although with the more prolonged follow-up this may prove to be too high, but there follows in the wake about 15 per cent of myxedema. It is not probable that Roentgen ray can duplicate this percentage of cures and if they did they would probably, just as in surgery, have a high percentage of myxedema. Fortunately or unfortunately, there is a limit to the amount of ray that can be used without injury to the skin and it is probable that the maximum

curative effect of Roentgen ray has been attained. Much as we may feel disappointed that higher percentage of cures goes hand in hand with an increase in myxedema, there is little question that this aftermath is less disabling than the original disease.

There is a rather large group of patients on whom I believe we are scarcely warranted in using Roentgen ray therapy. I refer especially to the severe types. As the beneficial results of Roentgen ray therapy rarely appear under eight weeks, it is a question whether such delay is warranted. A period of twelve weeks should elapse before we are at all certain Roentgen ray is not going to give results. In addition to the danger of increasing cardiac injury by this delay, there is also the financial loss from inability to work. It is, I believe, unwise in case no improvement appears after three months of treatment to discontinue the use of Roentgen ray.

In the milder types, where the patient is able to carry on at his work and where the probability of systemic damage from delay is light, Roentgen ray may be used. This, I believe, is a legitimate field for Roentgen ray therapy, as we are reluctant to submit such a patient to subtotal thyroidectomy with the danger of myxedema. We must also remember that this is the group with low surgical mortality. In any case, it is essential that even in the milder forms, prompt treatment by either surgery or Roentgen ray is vital, rather than trusting to chance for a spontaneous recovery.

The preparation of the patient for operation is a coöperative procedure followed by both physician and surgeon, who work together to determine the time when maximum improvement has developed. Plummer's discovery that iodine lessens toxicity and lowers operative mortality makes it desirable that the pre-operative iodine treatment is properly carried out. The much more palatable sodium iodide is just as efficient as Lugol's solution, which is converted into iodide after absorption. One cc. of Lugol's is equivalent to 150 mg. of sodium iodide. In case of persistent vomiting, the sodium iodide can be readily administered intravenously. It cannot be too strongly emphasized that the iodine is given only for the purpose of preparing the patient for surgery. If continued over a prolonged period, return of toxicity may occur and may fail to yield to further iodine therapy. It is also important that when iodine has been given it should not be discontinued until surgical measures have been carried out, as a violent relapse may result.

The question arises of continuing iodine after operation. The tendency at present is to continue its use for five or six weeks. Even in subtotal thyroidectomy, the small remaining tissue may become hyperplastic, with return of symptoms. Else¹¹ has recently advised that the long continued postoperative use of iodine will prevent recurrence. Clute and Lahey¹² report that the continued use of iodine does not prevent recurrence. This is in accord with our experience. It has been shown that if more than about two-thirds of the total

thyroid is removed in dogs, iodine will not prevent hyperplasia of the remaining portions. Apparently, this is also true in hyperthyroidism. Lahey, however, believes that very small doses of iodine are beneficial after the appearance of a recurrence.

Iodine is equally efficient in the hyperplastic and nodular type of goiter. This may be taken as evidence that the adenoma is not playing an active rôle in the intoxication.

The method of action of iodine is unknown. If the total capacity of the thyroid for iodine is less than 50 mg., the question arises as to why we should give such large doses. I believe it has not yet been actually determined that the massive doses, 1 cc. three times a day are essential or desirable. Certainly a large part of the iodine administered is never converted into the biologically active iodoglobulin, but is promptly eliminated from the body.

Much better remissions may be obtained if the patient is at rest during the iodine therapy. The length of time required to secure a satisfactory remission varies usually from eight to twelve days. Occasionally, a remission may be delayed and appear as late as three weeks. If the basal metabolism drops and then remains stationary for a few days, operation may be advisable even if the rate is still high. On the other hand, when little or no improvement is noted it may be advisable to continue the iodine for three weeks. Longer delay in hope of benefit is usually disappointing. About 5 to 10 per cent of patients fail to show an iodine remission.

The development of myxedema following any form of treatment is passed over rather lightly by some physicians. If recognized, it can usually be controlled if not entirely relieved. Lahey's experience, however, indicates that it is not a complication that can be lightly ignored. If the patient with this after effect falls into the hands of a physician who recognized the character of the trouble, well and good. Not all patients so afflicted will be so fortunate and failing to recognize the nature of their trouble may result in chronic invalidism.

There is little doubt that subtotal thyroidectomy is more successful in relieving hyperthyroidism than lobectomy. There may be, however, considerable difference of opinion as to whether every case should be submitted to this extreme procedure, with the possibility of acquiring myxedema. The less radical procedure followed for a quarter of a century is reported as curing 70 per cent of the patients, with very little of the danger of myxedema. Those not benefited could submit to a second operation, thus reducing the possibility of myxedema to this smaller group. Present experience suggests that there is a small group that can only be relieved of their intoxication by complete thyroidectomy. Here myxedema is unavoidable.

I believe it is unwise to be complacently satisfied with the present methods of treatment. Preventive measures should be further

investigated. Perhaps the physiologist and biochemist may soon solve the enigma of hyperthyroidism so that we may attack the cause rather than remove an organ which is possibly merely responding to some distant evil influence.

Conclusions. Our knowledge of the pathologic physiology of thyrotoxicosis is extremely limited.

In the present state of our knowledge, the term "thyrotoxicosis" is preferable to "hyperthyroidism." "Thyrotoxicosis with nodular goiter," is more accurate than "toxic adenoma."

We are greatly in need of accurate information about the end results of subtotal thyroidectomy. Such information cannot be obtained by a questionnaire. The patient must be carefully questioned and examined by a competent physician. As far as the writer has been able to determine, such a follow-up five years after operation has never been reported.

The present method of treatment may be the best that can be developed. It cannot, however, be considered highly satisfactory.

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A SIMPLIFIED METHOD OF GASTRIC ANALYSIS.

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In medical practice, the value of the analysis of the stomach contents has been much disputed. This is largely due to the fact that no simple and accurate test has been developed, and that the results obtained by the methods in general use have often not seemed of sufficient importance to warrant the time and labor necessary in carrying them out.

Many of the leading clinics of Europe have abandoned these methods and are using test-meal solutions to which an indicator has been added, thereby making possible accurate acid, volume and motility determinations. This work has largely been of an investi-

gative nature, and has recently been taken up by Bloomfield¹ in this country. Its application as a simple routine procedure in private and clinic practice would stimulate interest in gastric analysis and add materially to its dependability.

The test meals usually employed are of cereal foods, such as gruels, barley water and the well-known Ewald meal. The methods fall into 2 groups. In the first and most widely used, a single extraction of gastric contents is made at an interval after the introduction of the meal. In the second group extractions are made at intervals over a period varying from one and a half hours up to three hours. After the tube has been passed and the fasting contents removed, the test meal is given, which necessitates the removal of the tube in most cases as the patient may have difficulty in swallowing while it is in place. The tube is again passed and subsequent specimens collected. The technical disadvantages are that the tube often has to be passed twice, it frequently becomes clogged up with food particles, considerable saliva is swallowed, and an uncontrollable psychic stimulus is added to the direct stimulus to the gastric mucosa.

When we give an Ewald test meal, we not only introduce bread-stuff into the stomach but between 400 and 500 cc. of water. Every sample of gastric contents extracted following the meal, so long as any of it remains in the stomach, will contain a mixture of gastric juice and of the meal in unknown proportions. Also it has been shown that the amount of toast given will neutralize surprisingly large amounts of hydrochloric acid. Consequently the acid value determined for any given sample of 10 cc. will be lowered by the unknown amount of water present and by the buffer action of the cereal. The extent of the reduction of the acid values will depend upon two factors. After the meal enters the stomach, it has the power of neutralizing the acidity up to a certain point but after this free acid will remain in the stomach contents. The time required for neutralization is quite unknown, and if part of the meal passes out of the stomach quickly, probably less neutralization takes place. A more important factor, however, is the rapidity with which the stomach empties. As the meal passes out, and the stomach mucosa continues to secrete, there is an ever shifting change in the relative proportions of meal and juice until the stimulus has left the stomach, and there is no accurate way of estimating the rate of emptying and the consequent diminishing dilution of the juice.

A modification of the methods of Lanz² and Bloomfield¹ is proving practical as a simple routine procedure in the investigation of patients complaining of gastrointestinal disorders. The meal consists of 50 cc. of 7 per cent alcohol containing 1 cc. of a 0.1 per cent solution of phenolphthalein in 95 per cent alcohol. It is prepared by adding 1 cc. of the indicator to exactly 49 cc. of the alcohol just before administering the meal, although the solution will keep

several weeks after it is made up. This is a 2 to 1000 solution of the indicator, and consequently dilutions of 50 per cent and greater can be read with the Dunning colorimeter which is already in general use for kidney function tests. This colorimeter is standardized for a 1 to 1000 solution, so that a reading must be divided by 2 in determining the percentage of phenolphthalein in a specimen for gastric analysis removed after introducing an alcohol-phthalein test meal. Specimens containing over 50 per cent of the meal are rarely encountered, and can be diluted down in order to read them. Doubling the concentration of the indicator makes the standard colorimetric readings but $2\frac{1}{2}$ per cent apart instead of 5 per cent, and as a color shade may readily be seen to be between two standards, the error in the readings is only slightly over 1 per cent.

The technique of administering the meal is similar to that already in general use, except for the time at which the extractions are made. The patient should fast twelve hours, and be as quiet as possible during the test. A Jutte tube is passed and all the fasting contents is removed. This type of tube has proven far less disturbing to the patient than the Rehfuess tube with its larger perforated olive tip, and consequently minimizes psychic disturbances. The meal, warmed to body temperature, is introduced through the tube and two subsequent specimens are removed. For the first, 10 to 15 cc. are withdrawn twenty minutes after the meal, and the second is withdrawn forty minutes after the meal. All of the last specimen is removed and the total amount recorded. The specimens are tested for free hydrochloric acid immediately after their removal, and if achlorhydria is present the tube is not yet withdrawn. A solution of histamin representing 0.1 mg. per 10 kilos of body weight is injected subcutaneously. Gastric contents are removed thereafter until free hydrochloric acid appears or until three samples have been tested and found negative for free acid. A 1 to 1000 solution of histamin made up and sterilized by the autoclave for hypodermic use will keep at least a month.

The fasting contents and both the specimens removed after giving the meal are analyzed as in other methods of gastric analysis with the addition of the determination of the percentage of phenolphthalein present in Specimens I and II. They must be alkalinized with the minimum amount of 10 per cent sodium hydroxid in order to bring out the color, as an excess will cause them to fade out rapidly. These figures will represent the percentage of dilution of the gastric juice and also the exact proportion of gastric juice present in the second specimen. The true values may be obtained by means of a simple equation. The percentage of gastric juice present in a given specimen will be the difference between the percentage of phenolphthalein present and 100. One hundred over the percentage of gastric secretion present, times the titrated acid value will give the correct acid value for the pure juice. This may be readily deter-

mined from a graph. In this way, the percentage of dilution of the gastric secretion is easily calculated, which is not possible with any of the methods in general use. The gross characteristics of all the samples of juice are noted, the sediment from the fasting contents is examined microscopically, and the tests are carried out for occult blood, lactic acid and pepsin content as in the other types of analysis.

The alcohol-phthalein gastric test meal possesses many advantages, both in the technique of its administration and in making possible more accurate acid titrations and volume estimations. It is only necessary to pass the stomach tube once, as the alcohol is introduced through it into the stomach. This may be accomplished without the patient's knowledge thereby avoiding salivation and psychic gastric secretion. Samples of the stomach contents are readily removed, as there are no food particles to clog up the tube, and it is rarely necessary to filter them before analysis, as they are usually clear and colorless. The alcohol-phthalein solution has no buffer action on gastric acid, so there is no neutralization of acidity by the meal as with the cereal test breakfasts. It is a reliable and rapidly effective stimulus to gastric secretion.³ The presence of the indicator, phenolphthalein, makes possible the determination of the number of cubic centimeters of pure juice present and of the acidity of the pure juice, and also the rate at which the stomach empties. This makes feasible the desirable brevity of the test as it is not necessary to wait two or more hours for the maximum acid value (the value of the pure or almost pure juice) to make its appearance, and there is an accurate forty minute volume reading which may be of considerable importance.

The use of histamin in cases showing no free acid in response to ordinary stimuli adds time and labor to the test, but, when carried out as outlined, saves doing a subsequent analysis following the injection of histamin. Two types of achlorhydria are now well recognized. The first is not a true one. There is no acid response to the presence of the usual test meals, but the mucosa is still able to produce acid if a powerful stimulant such as histamin is injected hypodermically. The second type is a true or complete achlorhydria and in these cases the mucosa has completely lost the capacity to secrete acid. This differentiation is of both therapeutic and diagnostic value.

There are certain unavoidable sources of error with this method as there are with the others. It is impossible to estimate the amount of alkaline mucus secreted by the gastric mucosa, but an excess may be identified upon inspection. The mucus that is swallowed is usually aerated. Taking precautions against swallowing the alkaline salivary secretions cannot be too strongly emphasized, as they may alter the acidity materially and interfere with the titrations. Gross blood will also reduce acidity, and no value can be attached to the free acid determinations in cases of actively bleeding

peptic ulcers or neoplasms. However, the chief source of difficulty is the regurgitation of the alkaline bile-containing duodenal contents in the stomach, which may actually produce a pseudoachlorhydria. The likelihood of such a regurgitation is greatly reduced if the patient is quiet and free from psychic disturbances. Anxiety or retching on the part of the patient during an extraction will often produce a gush of bile into the previously clear gastric contents. It has been suggested that uncontrollable regurgitation through the pylorus often occurs quite freely minimizing the value of gastric analysis.⁴ It does occur, but usually carries bile with it to a lesser or greater degree, which is easily recognized and must be taken into account in judging results. Excess of bile has only been noted in 10 per cent of the cases, and then only in certain types of cases as a rule, notably neurotic individuals and those suffering from gall-bladder disease. As acid readings vary very little in repeated tests on the same subject, and as the clear specimens in a series of ten-minute extractions show no sudden drops in acid figures which regurgitation might well cause, it is difficult to believe that any material amount of regurgitation takes place clinically unless the tell-tale color of bile appears. If bile or blood is present in a sample, it is impossible to obtain an accurate phenolphthalein reading, but this has only occurred in both samples in 4 per cent in 150 cases. If bile does interfere with the analysis, the stomach may be washed out with water and the meal repeated with the probability that a second attempt will be successful, or else the test must be repeated on another day. Because bile appears at one trial, does not necessarily mean that it will appear at another. These disadvantages actually interfere with the results in only a very small number of cases.

There is a small group of cases in which the series of acid readings seem quite incompatible. The technique and results should be carefully scrutinized before the method of analysis is judged unreliable, because the normal and pathological physiology of the stomach vary surprisingly. There are cases which may show normal or even high acid figures in the fasting contents, and no free acid after the meal. Such a finding may be due to excess bile or mucus, but in rare instances is undoubtedly due to an open pylorus through which practically all the meal passes quickly, producing little or no stimulus to acid secretion. Occasionally there is a marked difference in the titratable acidity of the two specimens, which, if alkalinizing factors are eliminated, may represent a quick response to the stimulus with early emptying of the stomach, or a slow response and considerable gastric mucus.

Probably no test of gastric function which gives the maximum degree of information will ever prove sufficiently simple and brief to be applicable to routine clinical use. However, this forty-minute test has proven entirely adequate except in a very occasional case,

and deserves a thorough trial as a readily applied adjunct to ordinary diagnostic procedures.

Summary. 1. The methods of gastric analysis in general use give very unreliable acid and volume determinations and offer many technical difficulties.

2. The use of alcohol as a meal provides an adequate stimulus to gastric secretion and eliminates many technical difficulties.

3. The Jutte tube is more readily passed and causes less psychic disturbance than the Rehfuß tube.

4. The addition to the meal of an indicator such as phenolphthalein in known concentration makes possible the determination of the acidity of the pure juice and of the exact emptying time.

5. The Dunning colorimeter, which is in general use for renal function tests, can also be used for the alcohol-phthalein test meal.

6. The exact volume of juice present forty minutes after administering the meal can be calculated.

7. The use of histamin in cases of suspected achlorhydria is incorporated into the test.

8. The alcohol-phthalein test meal takes only forty minutes to produce the essential information in nearly every case.

9. The test is sufficiently simple and accurate so that gastric analysis should be more generally and effectually carried out.

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CLINICALLY PRIMARY TUBERCULOUS PERICARDITIS.

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TUBERCULOUS pericarditis has engaged the interest of clinicians and pathologists for various reasons—among others in a discussion over the possibility of its primary or secondary character.

That tuberculosis can occur in the pericardium and nowhere else in the body, seems to be established. Hedblom⁵ collected 13 cases and Rawls¹⁰ has since added another. Riesman² calls attention to the "clinically primary" type by which he means that active tuberculous lesions elsewhere in the body cannot be demonstrated at the onset of symptoms. Careful search in the literature has revealed only 11 such cases, in which the diagnosis cannot be ques-

tioned and in which the clinical history is given in enough detail to draw comparisons. In addition to these, 2 others are being added, both being on the same service at the Philadelphia General Hospital at the same time.

Case Reports.—CASE I. O. M., a male negro, aged twenty years, was admitted to Dr. Schnabel's service September 20, 1926, with a temperature of 102° F., pulse rate of 80 and respirations of 25 per minute, complaining of shortness of breath and pain in the epigastrium.

His parents were both dead of unknown causes. He had had one Neisserian infection, but no other illnesses that he could remember.

The history of his present illness is indefinite. He had quit work as a laborer in an iron yard three months before admission, because of weakness. There had been intermittent and mild pain in the epigastrium and at the time of the pain he would be short of breath. There had been some cough with a little expectoration and an occasional night sweat.

Physical examination showed an apathetic negro, breathing rapidly with marked working of the *alæ nasæ*. The chest gave a flat percussion note posteriorly from the fifth rib downward on both sides. Cardiac dullness was increased and was continuous with the pleural dullness. The heart sounds were muffled and no murmur or friction rub was heard. The pulse diminished in force during inspiration (*pulsus paradoxus*). The liver was enlarged and tender and there was some ascites.

Two days after admission, 540 cc. of clear fluid were removed from the left, and 1000 cc. from the right pleural cavity. In the next two days, 175 cc. and 1000 cc. of bloody fluid were removed from the pericardium. Following this, the *pulsus paradoxus* disappeared and a pericardial friction rub was heard for the first time.

There were 4,400,000 erythrocytes and 6700 leukocytes per c.mm. The urine showed a small amount of albumin and an occasional cast. Cultures of the blood, pleural and pericardial fluids were sterile. By staining methods, no tubercle bacilli were found in the sputum, nor in the sediment of the fluids removed from the pleura or pericardium. The Wassermann reaction was negative.

The Roentgen rays showed a much enlarged cardiac shadow and fluid in both pleural cavities. Neither in the pictures taken on admission nor in those taken subsequently was there any evidence of pulmonary tuberculosis.

Fever was present during his entire stay in the hospital. The highest recorded temperature was 103° F., and for the first six weeks of his stay it varied between this and 101° F. The first normal temperature was recorded six weeks after admission. During the next three months, there was a mild fever each day, the temperature rising to 100° or 101° F. The fluid in the pericardium increased in quantity and was only partially removed by thoracentesis. There were many times when this procedure failed, probably because the needle became plugged with fibrin shreds which were always present in the fluid. Dyspnea and edema, due to cardiac failure, varied with the success of the tapings. At one time the face, left breast and arms were very edematous.

During February and March, there was gradual improvement until he was able to be up and around the ward all day without discomfort, despite the fact that the cardiac dullness was still much greater than normal, and the temperature was between 99° and 100° F. He was discharged March 25, disappeared immediately and has not been heard from since.

Fluid removed from the pericardial sac on November 14 was injected into a guinea-pig. A necropsy on this pig on December 30 showed typical tuberculosis.

Case.	Sex and age.	Race.	Initial symptom.	Diagnosis based on.	Duration, mos.	Termination.	Highest fever.	Edema.	Dyspnea.	Cough.	Fluid removed,* cc.			Necropsy findings.
											Pericardium.	R. pleura.	L. pleura.	
Case I (O. M.)	M. 20	Negro	Pain in abdomen	Guinea-pig inoculation	9	Improvement; went home	103.0° F.	+	+	+	1255	1020	540	Tuberculous pericarditis; miliary tuberculosis; tuberculous glands.
Case II (C. A.)	M. 22	Negro	Cold	Guinea-pig inoculation	4½	Death	105.0° F.	+	0	+	2100	1100	700	Pericardium adherent; miliary tuberculosis.
Osler ¹	M. 32	White	Cough	Postmortem	5	Death	102.0° F.	+	+	+	0	0	0	Tuberculous pericarditis; miliary tuberculosis.
Osler ¹	F. 39	Negro	Dyspnea	Postmortem	5½	Death	103.0° F.	+	+	+	300	0	0	Pericardium adherent; right pleura adherent; healed tuberculosis of right upper lobe.
Hedblom ³	M. 36	White	Sore throat	Guinea-pig inoculation	15	Improvement; went home	101.0° F.	+	+	+	6500	0	700	Pericardium adherent; right pleura adherent; healed tuberculosis of right upper lobe.
Riesman ²	M. 32	White	Pain in shoulders	Guinea-pig inoculation	5	Death	101.0° F.	+	+	+	0	0	2850	Pericardium adherent; right pleura adherent; healed tuberculosis of right upper lobe.
Annaudrat ⁹	M. 13	White	Dyspnea	Guinea-pig inoculation	6	Cured	103.5° F.	+	+	0	300	0	+	Tuberculous pericarditis; miliary tuberculosis (liver); tuberculous glands.
Masselet ⁵	M. 30	Negro	Pain in chest	Postmortem	9	Death	?	+	+	≠	200	0	0	Tuberculous pericarditis; miliary tuberculosis (liver); tuberculous glands.
Jauch ⁷	M. 23	White	Fever	Postmortem	3	Death	103.6° F.	0	0	0	480	-600	-	Tuberculous pericarditis; miliary tuberculosis.
Ehrenclow ⁶	M. 18	White	Severe cold	T. B. C. stained in fluid	4½	Improvement; left hospital; later died	104.0° F.	+	+	+	300	0	750	Not obtained.
Rawls ¹⁰	M. 51	Negro	Dyspnea	Guinea-pig inoculation	4	Death	?	+	+	+	1000	0	0	Tuberculous pericarditis; died after artificial pneumopericardium.
Dillon ¹¹	M. 10	Negro	Dyspnea	Postmortem	5	Death	103.0° F.	+	+	0	0	0	0	Pericardium adherent; tuberculosis of spine; tuberculous endocarditis; miliary tuberculosis.
Renaud ¹²	F. 55	White	Grippe	Postmortem	22	Death	"Slight"	+	+	0	0	0	0	Pericardium adherent; healed tuberculosis apices of lungs; arthritis.

*Figures include both antemortem and postmortem removals.

CASE II.—C. A., a male negro aged twenty-two years, was admitted November 12, 1926, with a temperature of 102° F., pulse rate of 130 and respiration of 35 per minute, complaining of pain in the right chest.

His mother died of an unknown cause when he was eight years of age, and he knew nothing of his father. He had had smallpox in childhood and no sicknesses since, until his present trouble. This started with a "cold" and cough six weeks before admission. He stayed away from work as a laborer for four weeks, worked only one week when he caught another "cold" and then came to the hospital. The pain in the chest was not severe. He had had a cough and spat a little blood at one time. Two days before admission his feet had been swollen.

Physical examination showed a well-nourished young negro, lying flat in bed. He was coöperative and in no discomfort. There was evidence of some fluid in the right chest. Otherwise the lungs were normal. The cardiac dullness extended from the right nipple to the left anterior axillary line. The heart sounds were distinct, and neither murmur nor friction rub was audible. The liver could be percussed one finger's breadth below the costal margin. There was no ascites. There were two crusts on the left elbow, apparently the result of a slight abrasion.

After 700 cc. of bloody fluid were removed from the pericardium, a typical to-and-fro friction rub was audible over the body of the heart. The blood count was 3,980,000 erythrocytes and 6000 leukocytes to the c.mm. The urine had a specific gravity of 1.008 and neither sugar nor albumin were present. The Wassermann reaction was negative. There were no tubercle bacilli in the stained smear from either the sputum or the sediment of the pericardial fluid. A guinea-pig inoculated with this fluid showed tuberculosis when necropsied five weeks later.

On admission, the Roentgen ray picture showed a tremendously enlarged cardiac shadow, the left border being shown in the axilla. This and three subsequent pictures showed no evidence of pulmonary tuberculosis.

The same difficulties in withdrawing fluid were encountered in this man as in the other patient. The fluid, however, did not cause as much embarrassment to the circulation. There was decided improvement and for awhile he was able to be up and around the ward in a wheel chair. On December 29, six weeks after admission, a Roentgen ray picture showed a mottled shadow in the left upper lobe. Each subsequent picture showed more involvement of the lung tissue until, in the last picture taken February 6, it was impossible to see the outline of the heart. He became weak and lost weight rapidly during January and died February 13.

Fever was present until two weeks before death. It was of a type similar to that seen in Case I. However, the temperature was lower during the first six weeks although there was one reading of 105°. Soon after the first signs of pulmonary tuberculosis were found in the Roentgen ray picture, there was a period of greater fever, followed by gradual defervescence. During the last two weeks of life, the temperature was normal, probably due to weakness.

Necropsy. Miliary tuberculosis of the lungs, spleen, liver, adrenals, lymph glands and kidneys. This was farthest advanced in the spleen and lymph glands, where the normal tissue was almost entirely replaced by caseation.

The tubercles varied in size in the different organs. In the lungs they were the size of a dime, in the liver the size of a pinhead, while in the kidney they were microscopic. The pericardium contained 1000 cc. of bloody fluid. Both layers of the pericardium were thickened and covered with an exudate 2 to 3 mm. thick. There were no adhesions. The heart muscle was only slightly hypertrophied and the valves were normal. There were 600 cc. of clear fluid in the right pleural cavity and 900 cc. in the abdominal cavity.

Comment. These 2 cases and 11 from the literature are grouped together in the accompanying table. From this it will be seen that the outstanding features of this disease are cardiac failure with fever and great increase of the cardiac outline, with few or no symptoms referable to the chest. The onset is very insidious, the enlarged heart area being easily demonstrable when the person appears for treatment. The duration of the disease is long, the shortest case lasting three and the longest twenty-two months after apparent onset. It is not necessarily fatal. Of these 13 patients, 9 died, 1 made a complete recovery and 3 were discharged much improved, but with the heart still abnormal. (One of these subsequently died of a "relapse.") Of those that died, 2 showed decided improvement in the heart condition but later developed miliary tuberculosis, so that in 6 out of 13 there was a successful attempt at an arrest of the pericardial tuberculosis.

There were 11 men and 2 women, 6 negroes and 7 whites. Of the American cases, 5 were negroes and 4 were whites. The youngest was thirteen and the oldest fifty-five years of age. Shortness of breath was the symptom most constantly found, being present in all but 2, and 1 of these 2 had a respiratory rate of 35 per minute without discomfort. Cough and weakness were almost as constant. Pain was uncommon and occurred in only 3. It was located by one in the shoulders, by another in the chest and 1 had pain in the belly, probably from the liver. The leukocyte count was given in 4, the highest being 13,000 and the lowest 6000. Fever was a prominent symptom in all. There was no characteristic type or variation but in all in whom figures were available, it was 101° F. or over and in 6 it was 103° F. or over. Edema was present in 11 and edema of the face was especially mentioned in 3. Pleural effusion was present in 7, the left pleura being involved six times. The left was involved without the right four times. Ascites was present in 5. Fluid in all four serous cavities in our first case made us think that we were dealing with a polyserositis. However, the different character of the fluids soon corrected our error, that from the pericardium being bloody, while from the other cavities it was clear straw-colored. As in Riesman's case, the pleura may be involved in the same process as the pericardium.

From the pericardium, fluid was removed during life in 7 and was found postmortem in 2 others. In 4 (all autopsied) the pericardium was adherent. The fluid was bloody in all but 2, where it was "turbid" and "purulent." In 1, it coagulated on standing. The quantity of the effusion varied greatly, 50 to 2500 cc. being removed at a single tapping. Of the 4 who lived to leave the hospital, all had had fluid removed from the pericardium.

The diagnosis was proven from antemortem materials in 7. In only 1 case⁶ was it possible to demonstrate the tubercle bacillus in the pericardial exudate by staining methods. In the other 6, the

diagnosis was made by guinea-pig inoculation with fluid from either the pericardium or pleura. The guinea-pig test sometimes failed to show tubercle bacilli on the first inoculation, so that repeated tests should be made with different samples of fluid.

There were 9 necropsies. Miliary tuberculosis was present in 6. Chronic tuberculosis of the lungs was present in 3 but in 2 of them it was slight and considered inactive. In 4 others, the failure to find chronic pulmonary tuberculosis was commented upon. In Masselot's⁸ case the right lung was infiltrated by tuberculosis from the mediastinum outward, the apex being healthy. Caseous lymph glands in the mediastinum are mentioned in only 3 instances. Bone tuberculosis was present in 2. In 1,¹² there was a remarkable arthropathy of many joints, resembling that seen in chronic lung suppuration. The pericardium was greatly thickened, in some 1 cm. or more. There were no valvular lesions, and in only 1¹¹ had the tuberculosis extended to the endocardium. All 3 who died without the miliary form of the disease had marked evidence of cardiac failure. In 2 of these, the pericardium was adherent and the third died eight hours after a pericardial aspiration and artificial pneumopericardium.¹⁰ Considering the very large amounts of fluid which were tolerated in the pericardium (2500 cc. in Hedblom's case), it would seem that the danger of death from cardiac failure is not great, particularly in those with fluid. In 1 of Osler's cases, there was decided improvement in the general condition with a real gain in weight and yet at autopsy the pericardium was adherent. (The cause of death was miliary tuberculosis.)

Since we know, as a result of the guinea-pig inoculations, that tubercle bacilli are fairly numerous in the pericardial fluid, and since the incidence of miliary tuberculosis is much greater in pericardial tuberculosis than in tuberculosis elsewhere in the body, it is reasonable to presume that some of the infected fluid may return to the circulation. For this reason and for the comfort of the patient, it seems essential to remove the fluid. Paracentesis is not as easy as in other forms of pericarditis because of the thickened, necrotic condition of the membrane, floating fibrin shreds, and the thick consistency of the fluid itself, which may clot. There were many dry taps in the 2 cases here reported. When tapping fails, one should consider pericardotomy. In the above mentioned Case II, which ended fatally, we were under the impression, gained by repeated taps, either dry or yielding only small amounts of fluid, that the enlargement of the cardiac outline was due to hypertrophy and yet at necropsy 1000 cc. of fluid were found in the pericardium. Had a pericardotomy been done, it is conceivable that the bacilli would not have been forced into the circulation producing the miliary tuberculosis from which he died. Dyspnea is not a reliable guide to the amount of fluid present, as this man was at no time uncomfortable.

Tuberculosis should be suspected in every case of pericardial effusion, the more so if it is purulent or bloody. In the absence of fluid, cardiac decompensation with increase in the cardiac measurements and accompanied by decided fever over a long period, should cause tuberculosis to be suspected.

Summary. Death occurs in tuberculosis of the pericardium from either heart failure or miliary tuberculosis, the latter being the more common.

Miliary tuberculosis is much more frequent in this than in other forms of tuberculosis.

In most cases, fluid is present in the pericardial sac and this fluid contains viable tubercle bacilli.

This fluid should be evacuated frequently. When it is impossible to do this by paracentesis, a pericardotomy should be done.

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REVIEWS.

DISEASES OF THE GALL BLADDER AND BILE DUCTS. By EVARTS AMBROSE GRAHAM, A.B., M.D., Professor of Surgery, Washington University School of Medicine, St. Louis, etc.; WARREN HENRY COLE, B.S., M.D., Instructor in Surgery, Washington University School of Medicine, etc.; GLOVER H. COPHER, A.B., M.D., Assistant Professor of Surgery, Washington University School of Medicine, etc.; and SHERWOOD MOORE, M.D., Professor of Radiology, Washington University School of Medicine, etc. Pp. 447; 224 engravings and 8 colored plates. Philadelphia: Lea & Febiger, 1928. Price, \$8.00.

THIS book accomplishes two most desirable things: (1) It brings together in the English language, for the first time since Rolleston's "Diseases of the Liver, Gall Bladder and Bile Ducts," a digest of all the important knowledge regarding the human biliary system and (2) it summarizes, from the standpoint of its originators, the work thus far done in connection with cholecystography.

An enormous amount of research, stimulated to a large extent by Lyon's development of a technique for nonsurgical biliary drainage and Graham's own work on the roentgenologic study of the gall bladder, has been in process during the past decade. This has revolutionized many of our ideas regarding the physiology of the biliary tract and has put others on a firmer foundation. All of this work is covered in the treatise, and is given, in the reviewer's opinion, its due emphasis. For those interested in the original material in the literature the book will be found invaluable, since it gives complete references, as is most convenient, at the foot of each page. When controversial matter is encountered the authors' tendency has been to state the various opinions and the grounds on which they are based rather than to emphasize their own.

Cholecystography occupies the largest section of the book (106 pages) and under this heading are included its historical development, its technique and a full discussion of its diagnostic efficiency. A chapter is devoted to the tests of hepatic function and the final one to the surgical treatment of cholecystitis. This book will appeal to the internist, the surgeon, the roentgenologist and the laboratory worker alike.

T. M.

SERUM DIAGNOSIS BY COMPLEMENT FIXATION. By JOHN A. KOLMER, M.D., DR.P.H., D.Sc., LL.D., Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania and Member of the Research Institute of Cutaneous Medicine. Pp. 583; 65 engravings. Philadelphia: Lea & Febiger, 1928. Price, \$7.00.

THIS is essentially a summary of the clinical and laboratory investigations made by the author in serum diagnosis by complement fixation, not only in syphilis but likewise in the field of the bacterial, protozoal and metazoal diseases of human beings and the lower animals. These methods are also applied to the identification of blood and seminal stains, the detection of meat and milk adulterations and other soluble albumins. New methods are discussed along with practical applications, including numerous references to the investigations of other laboratory workers.

In Part I are stated the important principles of serum hemolysis and complement fixation. Part II deals with the principles of technique. In Part III is presented the technique of the author's methods in detail, while Part IV is devoted to an account of the sensitiveness, specificity and practical applications of methods in serum diagnosis and treatment of various diseases.

This work is to be recommended not only to serologists and laboratory technicians but also to practising physicians and veterinarians.

W. K.

GONOCOCCAL URETHRITIS IN THE MALE. FOR PRACTITIONERS. By P. S. Pelouze, M.D., Associate in Urology and Assistant Genito-urinary Surgeon, University of Pennsylvania; Fellow of the Philadelphia College of Surgeons. Pp. 357; 78 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, \$5.00.

ONE would like to see this book in the hands of every young man whose practice of medicine is going to cover the treatment of gonorrhea in the male, for much of the fundamental information contained herein is entirely unknown to the practitioner. The volume is divided into two parts. In the first 246 pages the principles underlying the diagnosis and treatment of disease are fully discussed. Part II consists of 48 cases illustrative of various types of infection. The first chapters (Applied Anatomy, Normal Histology, The Gonococcus, Pathology, Immunity, The Influence of Cell Type Upon Gonorrhea, Defensive Processes Against Gonorrhea) represent a logical, lucid theory of what urethral gonorrhea is, evidently based upon long experience in the clinic, in the laboratory and in the classroom.

Consider, for example, the admirable brevity of the following statements: "(1) Gonorrhea is a disease due to tissue penetration by the gonococcus. (2) The germs reach points that we admittedly do not reach without germicidal substances. (3) The deeper-lying bacteria outlast the stage of exudation, and are not greatly affected by the process of phagocytosis. (4) Under ideal conditions recovery may occur without any treatment whatever."

And the following: "1. The susceptibility to and tenacity of gonorrheal infection of the urogenital tissues bear a direct relation to the height of the superficial cells. The flatter the superficial cells, the harder they are to infect, and the more readily do they recover if infected.

"2. Stratification of cells is definitely protective. The fewer the strata of susceptible cells, the deeper is the gonococcal penetration and the greater and more prolonged is the inflammatory action.

"3. The susceptibility of transitional epithelium bears an inverse relation to the dilatability of the structure it covers. . . .

"4. Long mucous channels of small caliber, though lined with the most susceptible types of cells, rarely will become infected through continuity of surface.

"5. The tenacity of infection in all types of mucosæ bears a direct relation to the drainage possibilities of the surface involved.

"6. If absolutely and permanently blocked a small mucous crypt eventually will accomplish its own sterilization. In other words, to retain virulent infection for great periods such crypts must be able to empty themselves from time to time."

The author has introduced a chart system of studying the progress of the disease which must be a great assistance in teaching to students the reactions of the urethra to sexual, alcoholic or therapeutic traumata. He uses his charts to illustrate how the trauma of the treatment excites exacerbations of infection.

"As physicians it is probable that we seldom realize how much our therapeutic efforts commonly do toward prolonging instead of shortening this battle. Many of our forms of treatment are definitely devitalizing to an urethral mucosa that is crying for real help, and instead of helping we often hinder.

"At least 95 per cent of male gonorrheics in this country are being treated by the general practitioner. The vast majority of physicians will admit frankly that they really know little about the disease. This need not hurt their feelings very much because so many of the urologists are interested in surgery, and are not thinking gonorrhea, and do almost as many foolish things and call them 'treatment.' Our textbooks contradict themselves and one another, and in doing so they spread confusion. . . . If we love humanity this places upon us as humanity's physicians the necessity of getting very busy and finding out how to treat gonorrhea before the world crumbles from advanced age. . . .

"We should be in a position to see how hopelessly ridiculous are the claims of the manufacturers of gonococccides, based upon their action in the laboratory where conditions in no way resemble those in the urethral mucosa. . . .

"The first, the so-called oral plan of treatment, throws upon the patient and his reactive processes the entire task of curing the disease. . . .

"The second plan of treatment is unquestionably based upon the idea of slaying bacteria through direct local attack by some germicidal substance. It does not take into account any reactive powers the patient may be able to marshal, but winnows the chemical products of the world in the more or less vain hope of finding an ideal germicide.

"There is more evidence to suggest that both are wrong than that either is wholly right."

These quotations illustrate the vehemence of the author's opinions. He endeavors to justify the methods of treatment of which he approves in the following chapter in which he repeatedly condemns astringents but says: "The best single chemical that we now use is potassium permanganate in proper strength solution."

We shall not disclose the plot of the story further. It is impracticable to condense it.

Inasmuch as the author boldly pronounces himself at odds with all the prevailing methods of treatment, it would be vain to pick out items in his therapeutics which do not happen to appeal to the reviewer. In the main, we can agree with the author far more generously than he seems willing to do. His principles of treatment are undoubtedly right. But his objection to astringents, coupled with his devotion to potassium permanganate, forms a noteworthy conjunction. It is interesting to see that he no longer insists upon the close connection of cysts about the bladder neck with tuberculosis elsewhere in the body.

This treatise is healthy, original, vigorous. We can wish that it were not quite so personal.

E. L. K.

RENÉ THÉOPHILE HYACINTHE LAENNEC. A MEMOIR. BY GERALD B. WEBB, M.D., President, Colorado School of Tuberculosis. Pp. 146; 13 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, \$2.00.

AMONG the biographical reprints from the *Annals of Medical History* none is happier than this centennial sketch of Laennec, "greatest of physicians." Though perhaps some may hesitate to grant him this proud eminence, none can deny that the young Frenchman's figure is one of the most compelling in the history of

medicine. In this brief story of a short but brilliant life, bits of the biographer's philosophy crop charmingly out: "The father of Laennec was a person of excellent physique and sound health, consequently of a winning and joyous nature," but further on "this later Polonius" appears "with his infinite capacity for the unseasonable;" comparing Broussais to Laennec: "one fought passionately for an error, the other dispassionately for the truth." E. K.

RECENT ADVANCES IN CHEMISTRY IN RELATION TO MEDICAL PRACTICE. By W. McKIM MARRIOTT, B.S., M.D. Pp. 141. St. Louis: C. V. Mosby Company, 1928. Price, \$2.50.

THIS little book is a printing of the 1927 Series of Lectures before the San Diego Academy of Medicine. It is an attempt to sketch in a most elementary way some of the important bearings of chemistry upon body function in health and disease. It may serve to call the reader's attention to some of these applications of chemical theory and method. However, the absence of a bibliography prevents its serving as a guide to more detailed presentations. It indicates correctly the fragmentary character of the development of this field of knowledge, but it hardly serves to suggest to the reader how much, even now, thorough study of any part of this general field will reveal. J. A.

THE DETERMINATION OF HYDROGEN IONS. By W. MANSFIELD CLARK. Third edition. Pp. 717; 100 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, \$6.50.

FOR many years among the most valuable books in our laboratories of biological chemistry have been the earlier editions of this book. The extensions and additions in this new third edition are so fundamental as to make it essentially a new work. The author now includes a treatment of the theory of hydrogen ion in terms of the activity concept. His presentation of the thermodynamics necessary to grasp the concepts of free energy and activity are almost unique in their comparative simplicity and clearness. His chapter on the theory of Debye and Hueckel is the best introduction in English to this theory with which the reviewer is familiar. His discussion of temperature coefficients will clear for many a most obscure phase of the field.

He has made his book an introduction into the theory of solutions at a time when a grasp of this theory has become indispensable to the worker in biological chemistry, and he has used the new concepts

to give a sounder significance to pH. His new treatment of the bibliography will prove an invaluable guide for the worker entering any unfamiliar field in the application of pH methods. Finally, the book is written with a literary style of distinct charm and is permeated with a philosophy of science which will carry the reader on from page to page unwilling to postpone at least a glimpse of its treasures.

J. A.

ADDRESSES ON SURGICAL SUBJECTS. By SIR BERKELEY MOYNIHAN, (BART.), President of the Royal College of Surgeons of England. Pp. 348; illustrated. Philadelphia: W. B. Saunders Company, 1928. Price, \$6.00.

THE author of this most interesting collection of essays needs no introduction to the profession. These various contributions have been presented to the public previously, but having them bound in one volume is a distinct advantage. The book needs no critical review. It merely requires the calling of the attention of the profession to the fact that it is published. Its merits justify its popularity.

E. E.

BOOKS RECEIVED.

New Books.

Third Report of the Commission on Medical Education, October, 1928. Pp. 70. Willard C. Rappleye, 215 Whitney Avenue, New Haven, Conn., Director of Study.

A sane and thoughtful presentation well worth the perusal of all who are interested in medical education. Copies will be supplied gratis by the Director of Study.

*Problems in Surgery. University of Washington Graduate Medical Lectures for 1927.** By GEORGE W. CRILE, M.D. Pp. 171; 49 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, \$4.00.

Le Nefrosi. By ALESSANDRO ESPOSITO. Pp. 212. Milan: Societa Anonima Instituto Editoriale Scientifico, 1928.

Written to fulfil the need of a comprehensive review of the nephroses in the light of modern European and American studies.

*Modern X-ray Technic.** By ED. C. JERMAN. Pp. 260; illustrated. St. Paul; Minnesota; Bruce Publishing Company, 1928.

*A History of Pathology.** By ESMOND R. LONG, PH.D., M.D. Pp. 291; 55 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, \$5.00.

* Reviews of titles followed by an asterisk will appear in a later number.

Neurological Examination. *By CHARLES A. MCKENDREE, M.D. Pp. 280; 88 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, \$3.25.

*A Textbook of Pharmacology and Therapeutics.** By HUGH A. MCGUIGAN, M.D. Pp. 660; 43 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, \$6.00.

Medical Clinics of North America. (New York number—November, 1928.) Pp. 334; 64 illustrations. Philadelphia: W. B. Saunders Company, 1928.

Medical Record Visiting List or Physicians Diary for 1929. New York: William Wood & Co., 1929. Price, \$2.00.

*Total X Fotos.** By DE DENIS MULDER. Pp. 57; 38 illustrations. The Hague, Holland; G. C. T. Van Dorp & Co., 1928. Price, \$1.80.

Practical Poultry Management. By JAMES E. RICE, B.S. in Agr. and HAROLD E. BOTSFORD, B.S. Pp. 506; 307 illustrations. New York: John Wiley and Sons, Inc., 1928. Price, \$2.75.

*Idiosyncrasies.** By SIR HUMPHRY ROLLESTON, BART., K.C.B., F.R.C.P. Pp. 119. London: Kegan Paul, Trench, Trubner & Co., Ltd., 1928.

New Editions.

*Textbook of Pharmacology and Therapeutics.** By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S. Pp. 743; 73 illustrations. Ninth edition. Philadelphia: Lea & Febiger, 1928. Price, \$6.00.

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, M.D., M.A. Fourth edition. Pp. 998; 38 illustrations. Philadelphia: Lea & Febiger, 1928. Price, \$9.00.

This continues to be the most important work on the subject that we know of and truly indispensable to anyone treating diabetic patients.

Regional Anesthesia. By GASTON LABAT, M.D. Second edition. Pp. 567; 367 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, \$7.50.

Clinical Electrocardiography. By SIR THOMAS LEWIS, M.D., F.R.S., D.Sc. Pp. 128; 107 illustrations. Fourth edition. London: Shaw and Sons, Ltd., 1928. Price, 8s. 6d.

With the steadily increasing number of electrocardiographs in use, this booklet becomes of increasing value. As a supplement to the *Clinical Disorders of the Heart Beat* by the same author, it is invaluable to student and internist.

The Elements of the Science of Nutrition. By GRAHAM LUSK, PH.D., SC.D. Fourth edition. Pp. 844. Philadelphia: W. B. Saunders Company, 1928. Price, \$7.00.

Like virtuosos of song, the author makes another final bow after an interval of eleven years. As in the past, this book fulfills its aim "to review the scientific substratum upon which rests present-day knowledge of nutrition."

The Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN, M.D., F.R.C.P. Fourth edition. Pp. 209. New York: Paul B. Hoeber, Inc., 1928. Price, \$2.50.

The present revised and enlarged edition continues to be the best brief book upon this subject with which the reviewer is familiar.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Nomenclature of the Accessory Food Factors.—In 1913 Funk applied the term *vitamin* to a group of nutrient principles. Etymologically at this time the term was correct, as it was believed that the substances were chemically allied to the amines and that they were something connected with life processes. Subsequent studies have not borne out this belief as to amine derivatives, yet the term *vitamin* has persisted, spelled, however, without the “e” and indicating so far as an “amin” is concerned, nothing. As new vitamins were described, they were classified largely on the basis of their solubility and from a historical standpoint letters were assigned to these vitamins according to the sequence of their discovery. JONES (*Science*, 1928, 68, 480) contends that the term vitamin was incorrect to start with and that with a subdivision of certain of the vitamins, namely vitamin B, into different fractions, it is necessary to have a new nomenclature for these accessory food factors. He suggests that the group name be *advitant*, indicating the close association of the substances with life processes. A provisional name could be given, with the suffix *amin* retained, indicating the disease of which it is preventive. Thus vitamin D would be called *rachitamin* as a provisional name. When the chemical composition is known it could be called *rachitasterol*. In place of vitamin A or fat-soluble A, the provisional name should be *ophthalmamin*. The permanent name would not be given until the composition of the unknown substance was definitely known. This suggestion of the author is well worth employing in medical terminology. It would save considerable confusion and at the same time be definitely indicative of just what the particular *advitant* prevented.

Recent Cases of Undulant Fever in New York State.—The increase in the number of cases of undulant fever, notably in the South, has been recognized by numerous physicians. As a matter of fact, the United States Public Health Service, in a recent bulletin, has gone so far as to say that in rural communities undulant fever will soon be more important from a public health point of view than typhoid fever. As evidence of this increased recognition of the disease, whether caused by the *Brucella abortus* or *Brucella melitensis*, is a report by GILBERT and COLEMAN (*J. Infect. Dis.*, 1928, 43, 273) of some blood examinations made in New York State on a series of cases occurring in that community. The authors examined 213 blood specimens of individuals who had continued fever which gave no reaction to *Bacillus typhosus*. Sixteen of these were found to give positive agglutination reactions with organisms of the *abortus-melitensis* group. Of 19 blood specimens which were to be examined for evidence of undulant fever, 6 gave a positive reaction. In 2 cases the infection occurred in the course of laboratory work. The series is of interest not only from the epidemiologic standpoint, but also because of the brief report of the clinical course of these 26 different cases. Incidentally, it is of some interest that none of the patients had come into contact with cows or hogs, but 14 of them used raw cows' milk. In 9 instances apparently there was contagious abortion infection of the herd from which the milk was obtained. Without the agglutination reaction there was no question that many of these severe infections would have been diagnosed severe cases of typhoid fever, influenza or even tuberculosis.

SURGERY

UNDER THE CHARGE OF

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NORTHEASTERN HOSPITALS.

Fractures of the Upper End of the Femur.—SHAW (*Brit. J. Surg.*, 1928, 16, 120) asserts that fractures of the narrow part of the neck are due to an axial twist of the femur, an indirect violence. Fractures of the broad part of the neck and intertrochanteric fractures are due to direct violence over the trochanter or to outward leverage of the shaft when head and trochanter are fixed. Fractures of the acetabulum are due to force transmitted directly along the capitocollar axis by violence applied immediately below the great trochanter. This axis runs through the center of the head of the femur and the great trochanter. Fractures of the pelvic girdle may be produced by the application of slowly increasing powerful pressure over the trochanters.

Hodgkin's Disease and Lymphosarcoma.—COLEY (*Ann. Surg.*, 1928, 88, 641) declares that lymphosarcoma and Hodgkin's disease should no longer be regarded as absolutely hopeless from any method of treatment. These tumors are, as a rule, extremely radiosensitive and are likewise responsive in a remarkable way to treatment with the mixed toxins of erysipelas and *Bacillus prodigiosus*. It would seem logical to use the combined treatment, thereby securing the advantage of the local effect of radiation (radium or Roentgen ray) and the system effect of the toxins which have the power to reach hidden and remote glands, beyond the reach of radiation. These patients should be kept under the closest observation for a long period of time and treatment should be kept up periodically for a number of years, especially in those cases in which the disease was generalized when treatment was begun. Cases of lymphosarcoma so treated should show a cure or at least a complete control for a long period (five years or more) in a very considerable number of cases, that is, 10 to 15 per cent. Typical cases of Hodgkin's disease still show a very bad prognosis and permanent control can be expected in only a very small number of cases.

Cancer in and About the Mouth.—BLAIR, BROWN and WOMACH (*Ann. Surg.*, 1928, 88, 705) state that cases are grouped into fairly definite anatomic sites chiefly because of their relation to treatment and prognosis and to facilitate classification, history taking and presentation. The term "carcinoma of the jaw" was not used, because bone involvement is secondary and only incidentally influences treatment. Growths with wide extension or metastases are put in the group corresponding to the primary growth site. Neck tumors do occur in which no primary growth site can be determined, but the majority of them are metastatic from some unrecognized upper respiratory or digestive-tract growth. In arriving at a plan of treatment and prognosis, clinical and microscopic findings are considered together. No one criterion has been found to offer a basis of prognosis accurate enough to present a percentage play to the patient of his chances of life. Biopsies are done in most cases before treatment is begun, both for confirmation of diagnosis and for studying the relative degree of malignancy of the growths. There has been observed a type of growth that in clinical aspects is cancer, but in which the microscopic picture does not show the typical definition of cancer. These growths may cause great destruction if not treated at least locally as cancer. The degree of malignancy of prostatic-gland carcinoma followed fairly closely that of the primary growth. There may be no microscopic evidence of malignancy in the regional glands, but this does not necessarily mean that the glands are not affected. Though results are, of course, best in the cases where no carcinoma was found in the glands, there are cases in the series that show that undifferentiated carcinoma even in the glands of the neck, is not an absolutely hopeless situation. There is a high operative mortality 21.5 per cent; all but one of the deaths occurring in advanced cases where very radical operations had been done. The farther back in the mouth and pharynx the operation is carried, the higher the mortality. This is probably due to increased liability to respiratory infection.

THERAPEUTICS

UNDER THE CHARGE OF

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Intracardiac Injection of g-Strophanthin.—FLECKSEDER (*Wien. klin. Wchnschr.*, 1928, 41, 1253) reports strikingly favorable results in the restoration of the circulation from the intracardiac injection of doses of 0.5 to 0.75 mg. of g-strophanthin in cases showing extreme grades of circulatory failure due to collapse. The cases reported are those of severe intoxication by either morphin or lysol. Following the intracardiac injection of the warmed strophanthin solution the pulse which has been imperceptible rapidly returns and the heart beat becomes stronger, and within a few minutes to a few hours shows marked slowing. Initially, however, a period of rapid rate with irregular rhythm is often observed. In cases in which there is evidence of cardiac disease the method proved a failure. The author believes, therefore, that it should be limited to those instances of circulatory collapse which occur in patients with previously sound hearts, such as cases of severe intoxication and possibly those due to acute infection.

EDITOR'S NOTE.—The method as used by the author would certainly seem to be fraught with rather extreme danger to the patient, since in 1 or 2 cases the injection of strophanthin had been preceded by the intracardiac injection of fairly large doses of digitalis. However, since he is dealing with cases seemingly almost hopeless, such risks might be justified, although it is difficult to condone such a careless disregard of the synergistic actions of the digitalis bodies.

The Basis of Chemotherapy. SEIFFERT (*Klin. Wchnschr.*, 1928, 7, 1497) presents a very comprehensive review of the accumulated facts with reference to the mechanisms involved in chemotherapy, and concludes that chemotherapeutic effects are dependent upon numerous and significant reactions in which the host participates actively. Direct parasitocidal action is only a part of the total actions. There seems to be little doubt that the phenomenon of drug fastness is dependent upon the chemical structure of the chemotherapeutic agent employed. Experimental and clinical observations show that there is very little if any valuable direct parasitocidal action involved, although the existence of marked specificity indicates the importance of some direct biologic action. The effort has been made to show that chemotherapeutic results are dependent exclusively upon a mobilization of the defenses on the part of the host, that is, as a special type of nonspecific therapy. The peculiar nature of these actions is ascribable to the special chemical structure of the agent employed, and the apparent specificity of its effects may be ascribed to its structure on the basis of its being organotropic.

The Actions of Insulin on Damaged Heart Muscle. VON HAGNAL, VIDOVSZKY and GYORZI (*Klin. Wchnschr.*, 1928, 7, 1543) follow up their own previous observations and those of other investigators which indicated the existence of possible detrimental action of insulin upon the heart in patients with diabetes. The present investigation is concerned with the effects of this agent in nondiabetic patients showing evidences of organic cardiac disease. Each of these patients was observed carefully for a preliminary period during which electrocardiograms were taken and each was then studied electrocardiographically after the administration of a fixed dose of 20 units of insulin. In 37 investigations made upon 33 patients, including 1 diabetic with angina pectoris, the following abnormalities are recorded: Sinus arrhythmia, twice; ectopic auricular beats, 6 times; atrioventricular rhythm with atrioventricular premature beats, 9 times; ventricular premature beats, 14 times; auricular fibrillation, twice; conduction disturbances, twice; bundle-branch block, once. When compared with similar observations on numerous noncardiopathic diabetic patients the incidence of electrocardiographic disturbance is seen to be much greater in the latter than in the former group. The disturbances of rhythm are not relieved by the injection of large doses of atropin or by the intravenous administration of glucose. Increase in cardiac rate is also shown to be independent of the hypoglycemia produced by insulin, and there is evidence to show that it might be due to an increased production of epinephrin. Changes in the form of the electrocardiogram are probably due to a direct action of insulin on the heart muscle, since they are not relieved by the administration of glucose. That these changes observed from insulin are often not harmless is evident from repeated clinical observations, especially where large doses of insulin have been required, as in cases of severe diabetes and where coma is present. The authors suggest that the administration of insulin to patients with myocardial damage should be coupled with the administration of large amounts of carbohydrate and that in cases with coma intravenous injections of sugar should be given simultaneously with insulin.

The Treatment of Rheumatic Diseases with Bee-sting Toxin.—WASSERBRENNER (*Wien. klin. Wchnschr.*, 1928, 41, 1255) presents a brief preliminary report on the use of a purified toxin from the sting of bees in 121 patients presenting such conditions as sciatica, neuralgia, chronic arthritis and arthritis deformans. He finds that this agent gives satisfactory results particularly in the group of patients with resistant forms of neuralgia, especially sciatica. The toxin is so purified as to be entirely free from protein, and it differs further from native bee-sting poison in not producing hemolysis. The most satisfactory method of administration, so far as favorable results are concerned, seems to be by intracutaneous injection. The initial dose is 0.2 cc., which is slowly raised to a maximum of 0.5 cc. Such injections produce only mild to moderate local reactions and are practically free from systemic reactions. After the first injection subsequent ones are administered only when the local reaction of the preceding dose has subsided.

PEDIATRICS

UNDER THE CHARGE OF

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Unclassified Types of Splenomegaly in Children.—HITZROT (*Ann. Surg.*, 1928, 88, 361) presents 3 cases of splenomegaly in children in whom the spleen was removed. In each case a shower of nucleated red cells appeared immediately after the splenectomy, and in 1 case this condition has existed for fourteen years, the nucleated red cells remaining in a proportion of 5 to 1 in the differential blood count up to the time of this report. In all the cases a few nucleated red cells were present prior to the operation, but the high percentage following splenectomy seemed a peculiarly constant feature not present in other cases of splenectomy studied by the author. Another feature present in all 4 cases was the onset of the disease in the second year with the appearance of a peculiar tint of the skin, bluish-white sclera, vomiting, loss of weight, loss of appetite and weakness. The third feature of interest was the lack of growth and development in these children. This arrested development also was markedly altered after the splenectomy. Two of the patients, after a short interval, began to grow normally, and to develop the mental traits characteristic of their real age. At no time did any of these children show any symptoms characteristic of rickets. Syphilis as a factor in all these cases can be eliminated. In 1 case malaria may have been a possible factor. No intestinal parasites were found in any of the cases. In the spleens there were no hyperplasias of the pulp cells, the Malpighian bodies seemed normal and the capsule and the trabeculae were not thickened. There was no evidence of myeloidization and, except for a slight increase in the blood content, there were no significant symptoms. The structural changes in the spleen were slight and not characteristic of any definite clinical condition.

Clinical Results with Measles Streptococcus Toxin and Antitoxin.—FERRY, GORDON, MUNRO, STEELE and FISHER (*J. Am. Med. Assn.*, 1928, 91, 1277) present a joint report of the work done in several institutions. At the Children's Hospital, where the treated patients were controlled with an equal number of untreated patients under the same conditions, the computed actual protection following the use of 20 cc. measles streptococcus antitoxin was 88 per cent. At the Herman Kiefer Hospital, where the patients treated with 10 cc. of measles streptococcus antitoxin were well controlled with a much larger number of untreated cases, as well as a larger number of patients treated with 5 cc. of measles convalescent serum, the actual protection afforded by the measles streptococcus antitoxin was 42 per cent, as compared with 19 per cent of those cases treated with measles convalescent serum. At the Children's Convalescent Home, where the susceptible individuals

were picked according to their reaction toward measles toxin, the positive skin reactors being considered susceptible, the computed actual protection, when the cases were controlled with an equal number of untreated cases, was 67 per cent. The average computed actual protection shown in the three series of cases in the three institutions was 66 per cent, and at the two institutions where the dose was 20 cc. the average protection was 78 per cent. This was apparently far superior to the computed actual protection afforded by the measles convalescent serum which was determined in the same series under the same conditions and controlled with the same untreated patients. In the Children's Convalescent Home it was shown in 13 out of 13 cases that infection and recovery from measles changes a positive reactor to a negative reactor. This, with the fact that diluted measles convalescent serum will neutralize measles toxin, speaks in favor of the proof of the specific relationship of measles toxin from *Streptococcus morbilli* to measles, and argues in favor of the use of measles streptococcus antitoxin, prepared from this toxin as a protective measure against the disease.

Observations of So-called Influenza Infection in Children.—McLEAN (*Arch. Pediat.*, 1928, 45, 571) states that influenza is as much a seasonal disease as are measles and whooping cough. There is a direct proportion between the decrease in influenza and the increase in measles. The same is true of measles and pertussis. The complications of influenza are the same as those of measles. The complications depend on management, physical condition of the patient, age and climatic conditions. Younger children are more apt to have recurrences and relapses than older children. One attack during a season predisposes to relapses, recurrences and reinfections. Either age or repeated attacks from year to year seem to confer a certain amount of immunity. The disease, when transmitted from one individual to another has a tendency to produce the same type of infection. In 361 patients of all ages definite recurrence appeared in 119 or 32.8 per cent. The average number of days of recurrences in patients of all ages was forty-five years. During October and November asthmatic bronchitis is the predominating type of infection. In February and March the gastrointestinal type predominates.

Blood in the Stools of the Newborn.—BONAR (*Am. J. Dis. Child.*, 1928, 36, 725) found the benzidin test for occult blood positive in 29.38 per cent of 1518 stools of 109 newborn babies. Occult blood is found too frequently in the stools of the newborn to ascribe its cause to the usual sources. It should not be considered physiologic. Certain observations seem to warrant the assumption that the bleeding is due to an intense hyperemia set up in the upper portion of the small intestine by the first products of digestion, by the primary bacterial invasion or by both. More attention should be given to the initial diarrheas of the newborn, which appear to be another manifestation of the irritability of the bowel which occurs in the early days of life.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Comparative Hysterectomy Results.—As the general surgeons squabble over the relative advantages of cholecystectomy and cholecystostomy, so the gynecologists are still trying to standardize hysterectomy. The difficulty encountered in comparing different series of hysterectomies from different clinics is that not only are they done by different operators, but they are done for widely variant lesions and, therefore, comparisons are obviously unfair. In order to make a careful and fair comparison of the supravaginal, complete and vaginal hysterectomy, a study was made by BAUER (*Am. J. Gynec. and Obst.*, 1928, 15, 680) in the Presbyterian Hospital, Chicago, taking an equal number of each type of operation, performed upon patients with the same type of lesion and who were in apparently the same physical condition before operation. From his study he found that it is safer to remove the uterus by vaginal hysterectomy when it is possible to do so. No deaths occurred in this group and there is a definite decrease in the morbidity. Twice as many cases were afebrile in this group as compared to the other two types of hysterectomy. In regard to the abdominal types of hysterectomy he found an increase of 50 per cent in the morbidity when the cervix is removed and the average convalescence is increased by nearly four days. On the other hand, only one case in the group of supravaginal hysterectomies returned for removal of the cervix and that was for a benign polyp. He concludes that the routine removal of the cervix for fear that malignancy or other disease might develop does not seem to be warranted when one considers the increased morbidity incident to its removal; to which conclusion we heartily subscribe. We do not agree, however, that the vaginal approach is preferable to the abdominal as a general rule but only in the hands of those who have been trained in clinics where this form of approach has always been popular. In average hands we believe that abdominal supravaginal hysterectomy will give the best postoperative results and lowest morbidity. It is by far the commonest type of hysterectomy performed in our clinic.

Chancre of the Cervix.—In discussing this subject and in presenting their experiences with such cases, STOOKEY and ROBERTS (*Am. J. Syph.*, 1928, 12 212) state that the cases of primary syphilis occurring upon the cervix in their series have been diagnosed entirely in women who had early secondary syphilis without external evidence of a chancre. In short, the cervix has been carefully investigated in every case of early

secondary syphilis. In contrast to their conception of the classical picture of the initial lesion of syphilis, the results have been startling. The most striking finding has been the lack of definite areas of indurated ulceration and the presence of edema. This edema, they believe, is the most constant outstanding clinical observation in the diagnosis of a primary syphilitic infection in women. Histologically, cold edema presents all the characteristics of early syphilitic infection aside from the fact that there is no necrosis of tissue, or in other words, round-cell infiltration of the blood and the lymph spaces is productive of edema without definite ulceration. The edema characteristic of syphilitic infection pits on pressure, is cold to the gloved examining finger and shows no tendency toward suppuration or fluctuation. As a result of their observations they are convinced that the primary lesion of syphilis is extremely common upon the cervix and without clinical diagnostic characteristics. The subjective sensations produced by a chancre on the cervix are almost negligible. Pain is absent, discharge is scanty and hemorrhage is usually absent. If this contention of Stookey and Roberts is correct we will all have to change our conceptions of the clinical appearances of primary syphilis of the cervix. Their paper is well written and should be seriously considered because although syphilis is usually transmitted to the female by the vagina, those of us who have had many years of gynecological experience must confess that the typical chancre is rarely seen on the cervix.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Ethmoiditis in Infants and in Young Children with Accompanying Eye and Orbital Complications.—THEISEN (*Arch. Otolaryngol.*, 1928, 8, 386) in a study of 31 cases of ethmoiditis, found in the six youngest patients with sinusitis, eye or orbital complication. Their ages ranged from two to twenty months. The diagnosis of sinusitis in all cases was based largely on roentgenograms. Orbital complications, particularly orbital abscess, made radical operation on the ethmoid bone imperative. In such cases an external operation was performed. One child, aged six months, had acute ethmoiditis with orbital abscess and exophthalmos. An infant, aged ten months developed orbital abscess about ten days following the onset of nasal discharge which came from the ethmoids. A child, aged ten months, developed ethmoiditis followed by great swelling of the lids and inflammation of the eye, orbital abscess, exophthalmos, with infiltration and swelling in the inner canthus. An infant, aged twelve months, developed ethmoiditis, the lids became edematous and inflamed, chemosis of bulbar conjunctiva, no exophthalmos, localized infiltration and swelling of the inner angle of the eye. An infant,

aged ten months, developed ethmoiditis, ten days later orbital abscess and exophthalmos developed. In the cases of ethmoiditis in young children with external rupture, the rupture usually occurs at the inner angle of the eye, with the appearance of an infiltration and swelling. In young infants, spontaneous rupture may follow closely an acute ethmoiditis.

Infection of the Eye; Report of a Case of Anthrax of the Eyeball.—CLARK (*Int. J. Med. and Surg.*, 1928, 41, 436) treated a boy whose cornea was penetrated by a flying piece of rock. Shortly following this the boy became acutely ill with malaise, dry and parched skin, temperature 99.5°, pulse 98. The eye was inflamed and presented a yellow appearance with a greenish tinge extending over the iris and posterior cornea. All tissues of the eye rapidly became swollen and a small area of gangrene developed. The eye was enucleated with practically no bleeding. Bacteriological examination revealed anthrax bacilli. The organism was acquired from a baseball mitt, the wool padding of which was cultured and the anthrax organism found.

Corneal and Scleral Anesthesia of the Lower Half of the Eye in a Case of Trauma of the Superior Maxillary Nerve.—VONDERAHE (*Arch. Neurol. and Psychiat.*, 1928, 20, 836), observed a patient who suffered a comminuted fracture of the left malar bone. Six weeks after the injury examination revealed paralysis of the left abducens, anesthesia of the lower half of the left eye and the left side of the face, and weakness of the left masseter muscle. The cornea and sclera are reached by the short and long ciliary nerves from the ophthalmic division of the trigeminal, but the author believes from observation of this case that a great portion, if not all, of the sensory fibers to the lower half of the cornea and sclera are supplied through the superior maxillary division of the fifth nerve.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Irrigations with Aqueous Solutions. Their Effect on the Membranes of the Upper Respiratory Tract of the Rabbit.—Irrigation of the nasal fossæ with aqueous solution has been advocated for many years in the treatment of various lesions of the nose. As a rule, the potential disadvantages and untoward sequelæ of this almost universally practised procedure have not been recognized, although attention to them has been directed in a previous review in these columns ("A Harmless Mucous Membrane Irrigant"—FISCHER and BLEDSOE *AM. J. MED. SCI.*, November, 1927). As a first step in ascertaining the histologic changes of the nasal mucosa occasioned by irrigation, STARK (*Arch.*

Otolaryngol., 1928, 8, 47) conducted a series of experiments on 24 normal rabbits, using 8 others for controls. The rabbit was selected as the experimental animal because its nose is very similar to that of man, anatomically, histologically and physiologically. The irrigating fluids consisted of 0.9 or 2 per cent sodium chloride solution, or tap water—all at a temperature of 40° C. At necropsy, 75 per cent of the rabbits irrigated were found to have mucopurulent secretion in the nasal fossæ and in the paranasal sinuses. Almost half (45 per cent) of which showed a bilateral involvement of the sinuses. The reaction of the nasal mucous membrane was less marked to the isotonic solution than to the hypotonic or hypertonic. The macro- and microscopic mucosal changes consisted of hyperemia with leukocytic infiltration, increased glandular activity, and increased in the size of vacuoles and epithelial cells.

New Histopathologic Findings in the Ear in Lues and their Importance in the General Pathology of the Ear.—In the early studies of the histopathology of the ear, it was believed that the many characteristic findings for the various congenital and acquired aural diseases were known. With the increase of our knowledge, however, less certainty as to the specificity of these lesions was entertained. After mentioning the prominent histopathologic findings in otosclerosis, Paget's disease, cretinism and the "choked labyrinth," ALEXANDER (*Laryngoscope*, 1928, 38, 295) presented the histologic changes which occurred in the ears of 6 patients with acquired syphilis—all of whom had been examined clinically during their lifetimes. Some of the outstanding lesions consisted of gumma in the cochlear capsule, ankylosis of the stapes, obliteration of the cochlear window and aqueduct (all of which have been described in otosclerosis); marked ectasia of the inferior parts of the inner ear, as is seen in Paget's disease; the occurrence of fat in the internal ear similar to the picture observed in cretinism; different degrees of atrophy in Corti's organ and in the nerve ganglion apparatus, simulating the findings caused by arteriosclerosis; and complete or incomplete closure of the cochlear aqueduct as is found in a "choked labyrinth" caused by brain tumor. The author dwells on the possibility that otosclerosis may be caused by syphilis and suggests that antiluetic treatment be instituted as an active and prophylactic therapeutic agent. He concludes by emphasizing that great diminution in hearing can be caused by changes in the conductive apparatus alone, with no changes in Corti's organ or in the nerve ganglion apparatus—as was found in one of the reported cases.

Studies of Pathologic Tissue Removed from Chronically Infected Nasal and Accessory Sinuses.—In a preliminary report of the histologic changes encountered in a selected group of patients suffering from disease of the nasal and accessory nasal sinuses, MULLIN and BALL (*Ann. Otol., Rhinol. and Laryngol.*, 1928, 37, 128) tabulated the findings of 32 cases. For convenience, exclusive of neoplasms, the histologic changes were classified into four groups—edema, fibrosis, leukocytic reaction, and glandular hyperplasia or atrophy. No constant finding was present which would enable one to correlate a definite group of

symptoms with the pathologic lesions. In the asthmatic cases the histopathologic lesions and the symptoms were the most closely related, but even among these the findings were not constant. The most severe type of sinus infection, as judged by destruction of tissue and the polymorphonuclear leukocytic reaction, was found in cases of bronchitis and of cough without local pain. Certain changes were sufficiently constant, however, for their absence to permit a negation of the presence of a disease process in the sinuses.

A Further Discussion of Affections of the Optic Nerve Due to Sinus Disease.—In discussing the same subject COFFIN (*Ann. Otol., Rhinol and Laryngol.*, 1928, 37, 165) differs with Loeb's conclusion that the bacteria or toxins from the diseased sinus are borne either arterially or lymphatically direct to the nerve, claiming that the affection of the optic nerve is brought about mechanically by the disturbed circulation of the parts and that the changes in the nerve might as easily be produced by infection of a sinus most distant from the nerve. Coffin emphasizes another not generally recognized manner of disturbance of the optic nerve from sinusitis, namely, a phlebitis of the ethmoidal and ophthalmic veins. Clinical comparisons are made, and pictures are reproduced, to substantiate his ideas.

Ligation of the External Carotid Artery for Persistent Nasal Hemorrhage.—In cases of severe spontaneous, traumatic or postoperative arterial hemorrhage about the nose or throat, in which ordinary hemostatic measures fail, carotid artery ligation furnishes a formidable controlling procedure. As most of these regions are supplied by branches from the external carotid artery, ligation should be limited to it—particularly in view of the fact that less danger ensues than in ligation of the common carotid artery. After a consideration of the surgical technique involved, ABRAHAMS (*Arch. Otolaryngol.*, 1928, 8, 29) reports a case of serious recurrent nasal hemorrhage following an operation on the right ethmoidal and sphenoidal sinuses, wherein ligation of the right external carotid artery proved effective.

RETROSPECTOR'S NOTE.—The retrospector takes this occasion to mention a case of severe, persistent epistaxis from the left antrum following extensive fracture of the malar bone; in which recovery followed left external carotid artery ligation after all other attempts to control the bleeding had failed.

Radical Operation on the Mastoid. End Results in 100 Unselected Cases.—Stating that a radical mastoidectomy is successful when it prevents intracranial infection, stops or lessens aural discharge and offensive odor, relieves headaches and vertigo, and preserves the hearing, WHITE (*Arch. Otolaryngol.*, 1928, 8, 32) has found, in the analysis of the end results of 100 unselected cases, that the procedure is largely successful. Fifty-seven of the radical operations were completely successful and the remainder resulted in a decided decrease of discharge and odor. Only 3 had intracranial complications. The hearing was improved in 37, unchanged in 14 and lost in 49. It is interesting to note that the poorest results occurred in all cases in which the discharge

had existed for less than a year; and that the most favorable results were seen in those cases with a discharge of from five to fifteen years' duration. Tonsillectomy was beneficial. Headaches and vertigo were relieved in 84 and 70 per cent, respectively, of those individuals so afflicted.

The Histology and Pathology of the Articulation of the Auditory Ossicles.—In studying many microscopic sections of normal and pathologic aural states in Alexander's laboratory, DRUSS (*Arch. Oto-laryngol.*, 1928, 8, 56) observed that the normal articulations of the malleus and incus and stapes consist of four layers in each ossicle: bony, calcified cartilage, hyaline cartilage and a variable terminal layer resembling fibrocartilage, connective tissue, endothelium, and so forth. In his opinion, the articulation is not that of a real joint, but rather a type of symphysis between the two ossicles. Ankylosis of the ossicles was of comparatively frequent occurrence and may be classified in the group of normal and considered a phylogenetic variety. The articulations were seldom the site of pathologic lesions, due in all probability to the resistant capsule surrounding the joint. In only 1 case of the 37 examined, including 16 cases of suppuration of the middle and inner ear, was there also suppuration within the joint.

RADIOLOGY

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Roentgenologic Manifestations in Eighty-seven Cases of Gastric Syphilis.—In the records of the Mayo Clinic from 1913 to the present MOORE and AURELIUS (*Am. J. Roent. and Rad. Ther.*, 1928, 19, 425) have found 87 cases in which the evidence of gastric syphilis was convincing. Of the patients 60 were men, 27 were women. Predominance of the disease in the fourth and fifth decades of life was indicated by the fact that 41 of the patients were between thirty and forty years of age and 26 were between forty and fifty years; the youngest patient was twenty years, and the oldest sixty years of age. In most patients of the series there was marked loss of weight, epigastric pain or distress, vomiting, achlorhydria, anemia without cachexia, and rarely hematemesis (4 of the 87), these symptoms constituting the syndrome so frequently described. Based on the roentgenologic manifestations three major types were distinguishable: (1) prepyloric; (2) median or hour-glass; (3) diffuse. Seventy per cent of the cases were of the first or prepyloric type, in which the deformity adjoined the pylorus and

extended proximally in varying degrees. Almost without exception the defect was concentric and rather symmetric. As a rule, contraction was pronounced and the lumen narrowed progressively toward the pylorus, resulting in a spicular form of the barium shadow, although in many instances it was of tubular shape with constant diameters. Whether short or long, the contracted lumen pursued a straight or fairly direct course and was never markedly tortuous; occasionally its margins were quite smooth but more often they were slightly irregular. Second in frequency was the median type comprising 22 per cent of the series. In this type the pyloric and cardiac extremities of the stomach were not involved and the lesion was confined to the segment between them producing hour-glass deformity. As in the first type, the filling defect tended to be concentric and symmetric, and the lumen of the constricted area was relatively smooth. A notable feature in most of these cases was the great length of the constriction so that the shadow of the deformed stomach resembled a dumbbell rather than an hour glass. Only 8 per cent of the cases were of the third type, with such diffuse involvement that little of the stomach remained normal. Here again concentric contraction was dominant. Though obvious in all cases, it varied in degree and in one instance was so extreme that the distal three-fourths of the gastric lumen was represented by a scarcely visible thread of barium while the cardiac segment was reduced to a small pouch. All three types had features in common. Peristalsis was lacking in the deformed area and was seldom active in the unaffected portion. Gaping of the pylorus was observed frequently. Even with marked narrowing, gastric residues and dilatation above the stenosis were rare. Most important of all was the rarity of a palpable mass. Often there was a vague sense of resistance but only once was a tumor felt distinctly. Despite numerous simulants, such as cancer, hypertrophy of the pyloric ring and gastrospasm from extrinsic causes, the authors feel that the Roentgen diagnosis of syphilis is possible in a high percentage of cases. This disease is always to be thought of in cases with a long, central hour-glass, or prepyloric narrowing without a palpable tumor, or when a patient has a lesion resembling scirrhus cancer but is relatively young, or when the patient is neither cachectic nor greatly weakened notwithstanding extensive disease of the stomach.

Some Pseudovesicular Shadows and Other Pitfalls in Gall Bladder Roentgenology.—In the direct examination of the gall bladder without the aid of cholecystography, CASE (*Radiology*, 1928, 11, 1) is of the opinion that a small rounded ovoid shadow in the right upper quadrant, distinctly not caused by the inferior border of the liver or kidney, is in all probability due to something else than the gall bladder. This is shown by the fact that the shadow may appear in patients from whom the gall bladder has been removed and by the further proof that the gall bladder visualized by the Graham method does not coincide with the ovoid shadow mentioned. Case believes that this shadow is usually made by the first portion of the duodenum, or by one of the small lobes of the liver, or by the pyloric end of the stomach. The same explanations apply to the rounded, so-called "gall bladder impression" of the first part of the duodenum, formerly attributed to pressure of the gall bladder.

On the Relationship of the Ingestion of Fats to Emptying of the Gall Bladder.—SILVERMAN and DENIS (*Radiology*, 1928, 11, 45) were able to confirm Boyden's findings that the ingestion of cream and egg yolk together or separately produces appreciable emptying of the gall bladder. Nonemulsified fat (olive oil) had practically no effect on the shadow of the gall bladder. In none of the patients examined was there a great increase of fat in the blood at the time the gall bladder was emptying.

The Normal Cholecystographic Response.—In a series of 251 patients responding normally to cholecystography at the Mayo Clinic, and later operated on for various abdominal lesions, 19 per cent were found to have disease of the gall bladder. KIRKLIN (*Radiology*, 1928, 11, 34), therefore, points out that positive cholecystographic diagnoses have a higher percentage of accuracy than negative diagnoses. In 37 cases, or nearly 15 per cent of the series, definite cholecystitis without stones was found at operation, although the cholecystograms were normal in every respect; Kirklin thinks that the percentage of normal responses in such cases is probably higher than is generally believed. In only 10 instances were stones found, and these were mostly small and few in number. In conclusion, the author points out that while the gall bladder is believed to be sensitive to autonomic nervous influences, its behavior in the cholecystogram as observed in this series is apparently seldom affected by duodenal ulcer, chronic appendicitis, pelvic lesions and many other diseases of abdominal organs.

Cholecystography in the Late Months of Pregnancy.—Among seventeen primiparæ examined by LEVYN, BECK and AARON (*Radiology*, 1928, 11, 48) the intravenous injection of sodium tetraiodophenolphthalein produced no harmful effect on the mother, fetus, or the course of the pregnancy. In 10 the concentration of the dye and response to the Boyden meal were normal; in all these cases the gall bladder occupied a high position, and in 6 instances pressure defects in the shadow were demonstrable. The authors do not believe that the failure to obtain a shadow in 7 cases was due to pressure but leave the implication that it was due to disease of the biliary tract which was probably of metabolic origin. Morning sickness occurred more often in the patients in which no shadow of the gall bladder was obtained. It is suggested that during the entire course of pregnancy a properly balanced fatty meal be taken daily to stimulate emptying of the gall bladder and prevent stagnation of the bile with the precipitation of cholesterol and the formation of stones.

In the general discussion of the foregoing paper Sherwood Moore, who has been intimately associated with Graham in the development of cholecystography, said that the intravenous administration of the dye is perfectly safe both in pregnancy and during the puerperium. He had given the drug in this manner to 28 patients in the late months of pregnancy. On the other hand, Conyers, in further discussion, stated that he did not give the drug in cases of pregnancy, as several women had menstruated freely fifteen to twenty minutes after taking the dye, and a number of women had severe uterine cramps following the injection.

Roentgenologic Aid in the Diagnosis of Ileus.—CASE (*Am. J. Roent. and Rad. Ther.*, 1928, 19, 413) again shows that the widely dilated gas distended loops of bowel characteristic of ileus, are demonstrable with the Roentgen ray, and usually without the aid of a barium meal or enema. Roentgen ray study can be made at the bedside, disturbing the patient little if at all. In general, obstruction of the small intestine is indicated by irregular gas areas, mostly in the center of the abdomen, and gas collections over fluid levels, more broad than high. Usually the diaphragm is not elevated. Often the wall of the bowel is not seen, but when visible exhibits Kerkring's folds as a herring-bone effect. Sometimes the gas distended segments lie parallel to each other like the steps of a ladder. The method is of special value immediately after operation in abdominal cases, and, in the absence of dilated intestinal loops, the presence of ileus is to be doubted.

Tissue Changes after Salvarsan and Bismuth Injections.—LEESER (*Fortschritte a. d. Geb. d. Roent.*, 1928, 37, 486) describes 3 cases in which dense shadows were demonstrable in the pelvis after intramuscular injections of salvarsan or bismuth. The patients were children two or three years of age who had been treated for congenital syphilis. In 2 instances the injected drugs had evidently been completely absorbed and the shadows which remained were attributed to myositis ossificans set up by irritation. Whatever the cause of the shadows, they might easily be misinterpreted by the roentgenologist if he is unaware of the patient's history.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Tuberculoma of the Central Nervous System.—ANDERSON (*Arch. Neurol. and Psychiat.*, 1928, 20, 354) analyses 27 cases and reports: Average age in 22, 31.8 years; males, 77.7 per cent; solitary tubercles, 74 per cent; size of tumors ranging from 2 by 2 cm. to 4 by 8 cm.; location showed no predilection for either side but the majority of the lesions were supratentorial; the weight of the brain was not increased but the volume appeared generally larger than normal; meningitis was present in 77.7 per cent; tubercle bacilli were noted in the spinal fluid only once in the series; spinal fluid cell counts ranged from 2 to 320; as to incidence among tumors, tuberculomas constitute 15 per cent. He considers that the tumor syndrome may be present but is usually eclipsed by the signs of meningitis.

Lesions in the Brain and Death Caused by Freezing.—BENDER (*Arch. Neurol. and Psychiat.*, 1928, 20, 319) finds that in 1 human being, 1 guinea pig and 1 rabbit that were frozen to death, congestion and miliary hemorrhages in all parts of the brain. There was also marked pulmonary congestion. In the human brain the nerve cells also showed severe vacuolization. She considers these changes to be due to the forcing of the blood to the brain by the peripheral ischemia. The fact that the vacuoles did not occur in the nerve cells of the lower animals she considers due to their smaller size, their lower grade of specialization or to the shorter period of exposure to the cold. She takes issue with the common statements in the literature that the anatomic changes due to death by freezing are not distinctive.

Tumors of the Nervus Acusticus, Signs of Involvement of the Fifth Cranial Nerve.—PARKER (*Arch. Neurol. and Psychiat.*, 1928, 20, 309) finds signs of involvement of the fifth nerve in all but 1 of 53 proved cases of tumor of the acoustic nerve and these signs were second in importance to those of injury to the eighth nerve. Parasthesia was common and in 5 cases it antedated the symptoms of involvement of the eighth nerve. Anesthesia and weakness of the muscles of mastication were less marked. Disturbance of the corneal reflex was present in 5 cases. Pain occurred in 4 cases in 1 of which it was identical with that of tic douloureux. Because of the frequency of involvement of the fifth nerve and its early occurrence, the author considers a careful examination essential where symptoms suggesting a tumor of the acoustic nerve are present.

Studies in Epilepsy, the Fibrin Content of the Blood.—LENNOX (*Arch. Neurol. and Psychiat.*, 1928, 20, 345) reports the measurement of blood and plasma fibrin in 100 patients with epilepsy and finds the average concentration of fibrin in the plasma approximately 19 per cent above the average concentration for normal persons obtained by Foster. The concentration of plasma fibrin was abnormally high in 34 of the patients. In only 7 of these could the increase be accounted for by pyogenic or syphilitic infection and in the remaining 27 patients the cause of the increase was not apparent. He advises further investigation with simultaneous measurement of the speed of coagulation of the blood, of the sedimentation of the red cells and of the concentration of the other plasma proteins.

Acute Toxic Encephalitis in Childhood.—GRINKER and STONE (*Arch. Neurol. and Psychiat.*, 1928, 20, 244) present a clinicopathologic study of 13 cases. They review the literature on the subject. Five of their cases occurred with severe neurologic symptoms and a definite focus of infection; 2 with severe neurologic symptoms and a fulminating septicemia; 1 with severe neurologic symptoms of undetermined origin; 2 without severe neurologic symptoms with focal infection; 1 occurred with scarlet fever. All the above came to necropsy. Two additional cases with neurologic symptoms and of focus of infection recovered. The postmortem observations formed a fairly uniform group. Macroscopically, the brain showed hyperemia with engorged leptomeninges,

the subarachnoid space slightly distended with fluid, and the cut surfaces reddened and studded with visibly dilated vessels. The authors do not consider the macroscopic appearance of hyperemia as pathognomonic of encephalitis. The important findings microscopically were the absence of mesodermal infiltration, a profound destruction of ganglion cells, and changes in the local vascular system consisting of new vessel formation and stimulation of the vascular endothelium often leading to obliteration of capillaries. There was also a marked proliferation of the glia cells quite constantly found consisting mainly of cystoplasmic glia and oligodendroglia with few Hortega cells and no free mobile glia cells. The microorganism recovered from the focal infections or from the blood was a staphylococcus or a streptococcus. The focus of infection constituted in most instances the initial complaint. Spinal fluid examinations were entirely negative excepting in one case. The infections encountered were usually those of the upper respiratory tract, infections of the ear and mastoid, pneumonia, scarlet fever and septicemia. The clinical course they found fairly uniform: "rapidly developing symptoms of diffuse cerebral involvement, often associated with meningeal symptoms; early stupor; hyperpyrexia and death in from three to four days." They believe the toxic agent exerted its influence by a hematogenous route. The suggestion is made that severe neurologic sequelæ may develop from acute toxic encephalitis associated with acute infections if recovery occurs and that more attention should be directed to encephalitis as an etiologic factor in these sequelæ.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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"Filtrable Forms" of the Tubercle Bacillus.—In recent years a very great interest has been aroused in the question of filter-passing forms of the tubercle bacillus, and the European, particularly the French, literature is filled with papers on this subject. COOPER and PETROFF (*J. Infect. Dis.*, 1928, 43, 200) in a critical review of the rather confusing reports have indicated certain possible or probable errors in technique and have added a number of observations of their own. Two angles of the problem are particularly discussed. The first is the filtration of various tuberculous materials through Chamberland and other filters and the inoculation into animals of, and attempts to obtain growth from the filtrates. Very rarely indeed was either a positive culture or a positive tuberculous process obtained in the guinea pigs and these that did occur may have been the result of a chance passage of the filter by the whole tubercle bacillus. However, the mass of evidence supporting

the occurrence of the filtrable forms has been the finding of acid-fast rods in the swollen, but not caseous, lymph nodes and the development of cachexia in the inoculated animals. The first observations are greatly weakened in their significance by the finding of acid-fast organisms in the lymph nodes in 33 per cent of normal or at least uninoculated guinea pigs by the authors and the development of cachexia is known to follow inoculation of foreign proteins, and may be the result of intercurrent disease and infections such as in the middle ear or the sinuses. The second angle of the problem is concerned with the possible passage of the filtrable form from mother to offspring. The general evidence is that tubercle bacilli are transmitted very rarely from mother to offspring when the placenta is perfectly normal and free from tuberculosis. Moreover, placental tuberculosis is not nearly as rare as is generally supposed and that in clinically active tuberculosis it is very probable that the permeability of the bloodvessel wall may be so altered as to permit, without actual placental infection, the escape into the fetal blood of intact whole organisms. These suggestions indicate that congenital tuberculosis when it does occur can be explained without the involvement of filtrable forms of the bacteria. There is little known about the life cycle of the tubercle bacillus and the occurrence of filtrable forms should not be ruled out if the evidence is satisfactory, but at present it is not necessary to accept the hypothesis of filtrable forms to explain the facts at hand.

The Dick Test and Allergy.—The skin reaction to the toxin of the scarlet fever streptococcus is so irregular following antigen administration that HARDY (*Proc. Soc. Exper. Biol. and Med.*, 1928, 25, 725) believes the explanation is to be found not in toxin reaction and anti-toxin production but rather in considering the phenomena as examples of allergy. A negative Dick test may signify that an individual has not yet been sensitized, or has been sufficiently stimulated to have developed circulating antibodies, which mask the allergy.

Regional Vaccination.—General vaccination by subcutaneous injection has been rather disappointing as a curative measure in many infections. Local vaccination as advocated by Besredka has been receiving recently an increased attention and now POINCLÔUX (*Comp. rend. Soc. de biol.*, 1928, 99, 287) advocates a third method of immunization—vaccination at the portal of entry or regional vaccination, using the word regional to include the tissues at the portal of entry of the pathogenic germ and the organ in which the germ has become established and is doing damage. He reports, in gonococcus and other infections of the cervix uteri, that with minimal amounts of auto vaccines (5 drops) he obtained a violent reaction and favorable results only when he injected his vaccine at the actual portal of entry. Further reports on the application of this principle of treatment (Poincloux and Weissmann, *idem*, p. 290) gives the results in patients with salpingitis, three infections by the gonococcus and one by the colon bacillus; in many patients with metritis (*idem*, p. 374) and in two with chronic gonorrheal urethritis and one with acute gonorrheal rheumatism (*idem*, p. 469). The benefit from this method of treatment was very encouraging.

HYGIENE AND PUBLIC HEALTH

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An Epidemiological and Statistical Study of Tonsillitis, Including Related Throat Conditions.—COLLINS and SYDENSTRICKER (*Pub. Health Bull.*, No. 175, July, 1927) present an exhaustive statistical study. The more important points in the summary are as follows: "Tonsillitis and other throat conditions appear to constitute 5 to 10 per cent of the measurable illness from all causes and from 15 to 20 per cent of the illness due to respiratory diseases. Cases of tonsillitis and sore throat seem to be much more frequently accompanied by general symptoms such as fever, aching, chilliness, and constipation than cases of coryza or bronchitis. The incidence of tonsillitis and related conditions of the pharynx is higher among children of school ages than before or after those ages. Laryngitis, on the other hand, appears to occur more frequently among adults than among preschool or school children. tonsillitis and related conditions of the pharynx appear to be the only important respiratory affection which shows this particular age incidence, that is, higher during the school ages than among younger or older persons. The incidence of tonsillitis and related conditions of the pharynx appears to be considerably higher for females than for males. Unlike other respiratory conditions, the reported incidence of tonsillitis and related throat conditions apparently does not increase during periods when influenza is epidemic. Nor is there evidence of important independent epidemics of tonsillitis and other throat conditions, except septic sorethroat. There is, however, a fairly regular seasonal variation in the incidence of these diseases. Tonsillitis and related throat conditions are relatively unimportant as causes of death. In about 75 per cent of the deaths in which some disease of the pharynx is involved, some other cause is specified either as the primary or a complicating cause of death. The most common diseases certified as joint causes with diseases of the pharynx are, in the order of their frequency, heart disease, pneumonia, septicemia, nephritis, rheumatism, bronchitis and tuberculosis. The frequency of tonsillectomy varies greatly in different sections of the country. In general, the more urban the district the more tonsillectomies are performed. Tonsillectomy rates in the Army and Navy are five to ten times as frequent now as they were about 1910. Tonsillectomy does not account for all the decrease in the prevalence of defective tonsils with increasing age. The incidence of certain nonrespiratory diseases varies with the condition of the tonsils.

The incidence of illness from rheumatism, heart conditions, cervical adenitis and ear conditions tends to be lowest among children with normal tonsils, higher among those with defective tonsils, and highest of all among those with removed tonsils. Presumably these more or less chronic conditions clear up only slowly, if ever, after the tonsils have been removed. For this type of condition, special treatment in addition to the removal of the tonsils may be necessary. The incidence of illness from rheumatism and related conditions appears to be higher among adults who have attacks of tonsillitis than among those who are free from tonsillitis. The incidence of diphtheria among children with defective tonsils seems to be much higher than among children with removed tonsils. Among children with normal tonsils it appears to be only slightly higher than among those whose tonsils have been removed. The incidence of measles, whooping cough, chickenpox, and mumps all appear to be higher among children whose tonsils have been removed than among either of the groups with the tonsils present. Similar differences are indicated by rates based on susceptible children only, eliminating from consideration all children who had suffered a recognized attack of the disease prior to the period of observation. A higher proportion of children with removed or normal tonsils were judged on clinical evidence to be of excellent or good nutrition than in the case of children with defective tonsils. However, the hemoglobin index in a small group of children did not reveal any difference among the various tonsil groups with respect to nutrition as indicated by this index. Height and weight measurements and records of growth in weight over a period of nine months for a group of school children did not show any advantage in the growth of one tonsil group over another."

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 19, 1928

The Nature of the Hyperglycemia Associated with Anaphylactic Shock in the Dog.—ISOLDE T. ZECKWER and J. ERNEST NADLER (from the Department of Pathology, University of Pennsylvania). It has recently been shown that hyperglycemia accompanies anaphylactic shock. The present study is an attempt to determine the mechanism of this phenomenon, and to gain further data on the factors which are involved in the release of glycogen from the liver. The experiments were carried out on dogs because of the apparent absence of the asphyxial factor in anaphylaxis in this animal. The dogs were divided into two groups: (1) intact animals, and (2) dogs in which the left adrenal had been excised and the right splanchnic nerve cut long previous to the acute experiment. Both groups of animals were sensitized to horse serum.

At the time of the acute experiment, the dogs were given amytal as an anesthetic which has little effect on the blood-sugar level; artificial respiration was instituted to offset any respiratory disturbance; blood pressure was recorded; and frequent blood-sugar determinations were made preliminary to the induction of anaphylactic shock by the injection of serum, and at frequent intervals after onset of shock.

Nine unoperated dogs showed a rise in blood sugar during shock, the mean increase above the preliminary level being 0.057 ± 0.006 gm. Six dogs which had been operated upon showed a relatively lower hyperglycemia, the mean increase being 0.026 ± 0.004 gm. In the latter, determinations of liver glycogen at the end of the experiment proved the presence of available glycogen.

Determinations of the oxygen content and percentage unsaturation of the arterial blood before and during shock ruled out the possibility that the hyperglycemia was due to inadequate ventilation.

The rise in blood sugar, which occurs in spite of the loss of adrenal activity, is considered probably due to the venous stasis of the liver, which is a conspicuous feature of canine anaphylaxis, because this rise in blood sugar can be simulated in the normal nonsensitized dog by mechanically constricting the hepatic veins for a brief interval.

The conclusion is made that there are two factors responsible for the hyperglycemia associated with anaphylaxis: (1) Sympathetic stimulation by way of the splanchnic nerves, involving the activity of the adrenals, and (2) glycogenolysis, resulting directly from venous stasis of the liver.

The Form of the Action Potential Wave in Nerve.—W. R. AMBERSON and A. C. DOWNING (from the Department of Physiology, University of Pennsylvania). We have confirmed the observation of ZOTTERMAN (*J. Physiol.*, 1928, 66, 181) that the electric response, produced by two action potential waves in close succession, does not reach a full doubling of that given by a single wave unless the time interval between the waves is greater than 50 sigma. We secure full doubling of the response, as measured by the maximal deflection of a highly sensitive Downing moving-magnet galvanometer, only when the stimulus interval is greater than 100 sigma, at temperatures above 15°C. , or greater than 150 sigma at lower temperatures.

The explanation of this long delay in recovery of the electrical properties has, we believe, been secured in a study of photographic records of the form of the galvanometer deflection produced by a single action potential wave, or by two waves in close succession. In a freshly excised nerve the form of the deflection given by the single nerve impulse differs radically from that produced by a break induction shock. When the nerve is in air, and above 15°C. , this difference consists (1) in a prolongation of the time necessary for maximal deflection, indicating a persistence of "negativity" for at least 100 sigma, and (2) in a later swing to the other side of the physical zero, indicating a more delayed development of an "after-positivity," which may continue for several seconds. These persistent elements of the action potential wave are of such low voltage that they can give almost no evidence of their existence in records taken with more rapidly moving but relatively insensi-

tive instruments, such as the string galvanometer or the various oscillographs. They persist for such a time, however, that their total electrical discharge may be considerably greater than that given by the well-known initial electrical discharge at high voltage. We believe that interference between the second action potential wave and these persistent remnants of the first is responsible for the long delay in recovery observed in our earlier experiments.

The character of these persistent potentials is easily modified by various factors. After long inactivity of the nerve they tend to disappear, so that finally the deflection given by the action potential wave may be almost identical with that given by a break induction shock. They reappear when the tissue is repeatedly stimulated and become the more evident, the greater the preceding activity. In air, and above 15° C. the "after-positivity" is always present, but this element of the action potential wave completely disappears upon the application of low tensions of CO₂ or of expired air. In such an atmosphere the persistence of negativity becomes very marked; in the extreme case we have seen it endure for thirty seconds.

By curve analysis altogether similar to that which is used in modern myothermic studies the time relations of the potentials producing the deflections can be approximately determined. Our evidence indicates that, when two or more impulses follow each other at short intervals, these persistent E. M. F.'s may be partially summated. Their intervention in central nervous phenomena, therefore, seems possible. Their easy and rapid modification by changes in conditions which at least simulate physiologic states suggests that they may have functional significance.

The Effect of Valence on Cellular Permeability to Water.—BALDWIN LUCKÉ and MORTON MCCUTCHEON (from the Laboratory of Pathology, University of Pennsylvania). When a cell, such as the egg of the sea urchin, is placed in a solution hypotonic with respect to its natural medium water enters under the driving force of osmotic pressure and the cell swells. The rate of entrance of water, per unit of time, per unit of surface, and per unit of pressure may be defined as the permeability of the cell to water, and depends on a number of factors such as temperature and composition of the medium (*J. Gen. Physiol.*, 1928, 12, 129). In the case of the spherical egg of the sea urchin, *Arbacia punctulata*, the osmotic swelling proceeds relatively slowly and permits accurate measurements of the diameter, from which volume and surface of the cells can be calculated.

In the present experiments the cells were placed in hypotonic solution of dextrose to which had been added the salt to be tested. Two series of experiments were undertaken: One with a group of cobaltamine chlorides, in which the valence of the cation ranged from 1 to 6, and one with potassium salts in which the valence of the anion ranged from 1 to 4, or 1 to 3, respectively. It was found that permeability to water is regulated, at least in part, by the sign and the number of changes on the ions in the medium, in the sense that cations decrease and anions increase permeability to water; and these effects increase rapidly with the valence of the ion. It was further shown that it is possible to

determine the concentration of a cation which will oppose the effect of an anion in its tendency to increase permeability to water, and conversely, the restraining action of a cation on osmosis may be balanced by the proper concentration of an anion.

Water and Chlorid Balances in Pneumonia.—J. H. AUSTIN and F. W. SUNDERMAN (from the Department of Research Medicine, University of Pennsylvania). The water balance was measured before and after the crisis in a series of 5 cases of lobar pneumonia by means of daily weighings of the patients and weighings of ingesta and egesta. The picture is predominantly one of a negative water balance in both periods. The caloric intake was small, especially before the crisis, at which time there was a daily negative nitrogen balance from 10 to 20 gm. If the performed water from metabolized tissues and the water of oxidation from these tissues are considered in connection with the water balance then there would appear to be a tendency toward increase in the percentile water content of the tissues before the crisis and a decrease following the crisis.

Our chloride-balance studies may be divided into two groups: the first consisting of 4 patients under the ordinary régime in which the daily chloride intake averaged between 1 and 1.5 gm. NaCl; and the second consisting of 3 patients receiving from 15 to 30 gm. NaCl daily before the crisis. The first group excreted more salt than they ingested during the precritical period, whereas the opposite occurred in the second group. The precritical low Cl excretion in our pneumonia patients was a consequence of the low Cl intake and under the ordinary régime the Cl balances were negative rather than positive.

Notice to Contributors.—Manuscripts intended for publication in the *AMERICAN JOURNAL OF THE MEDICAL SCIENCES*, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

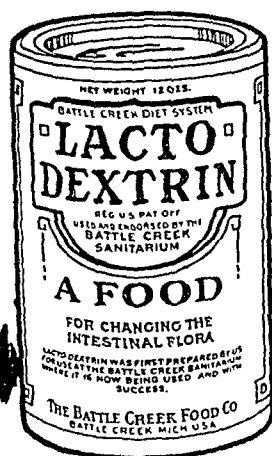
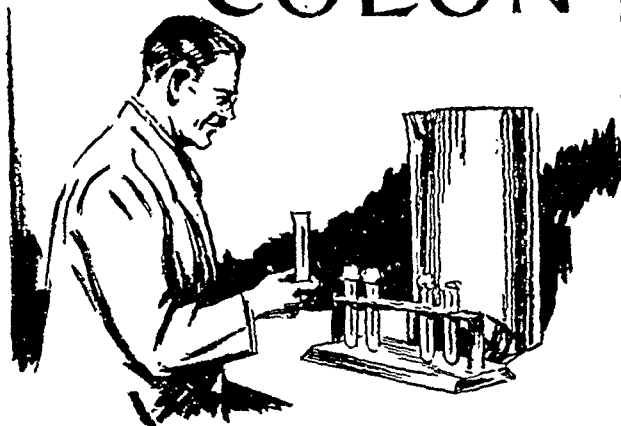
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No. 3

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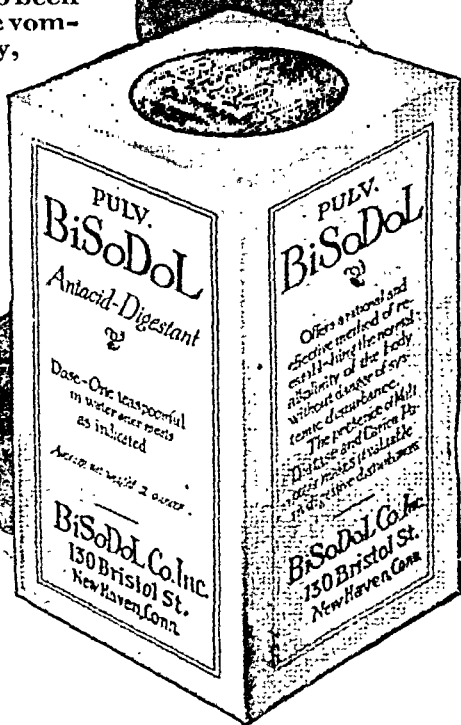
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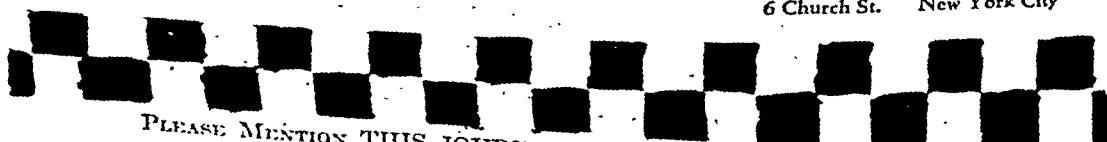
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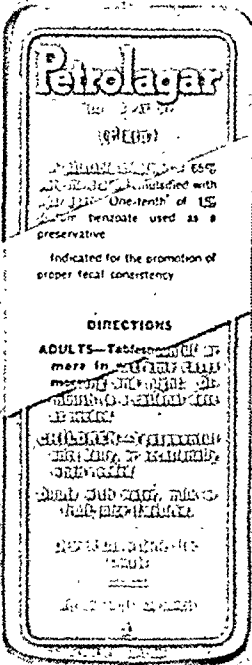
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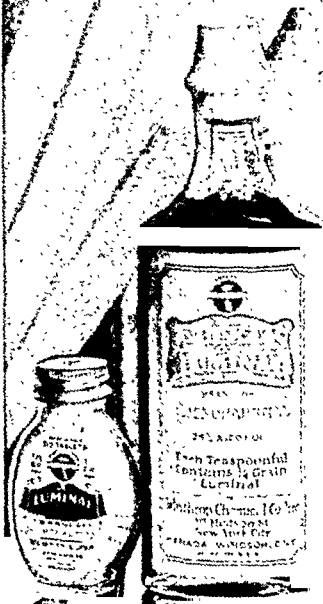
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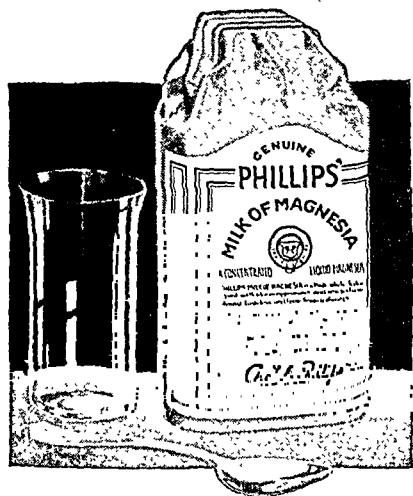
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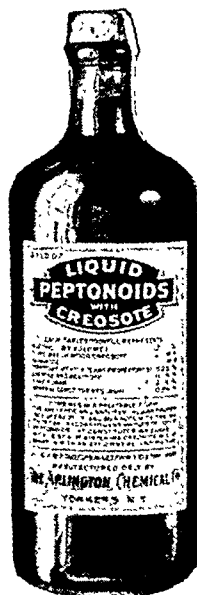
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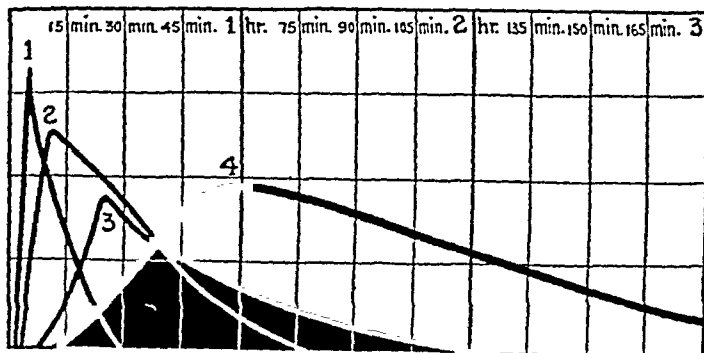
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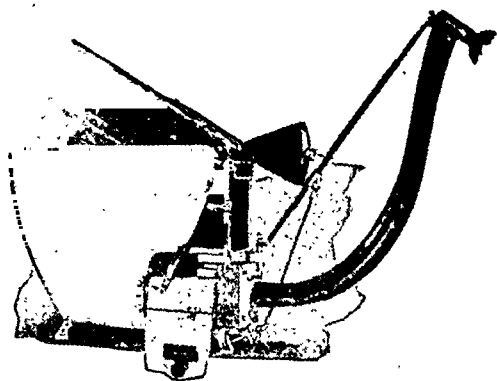
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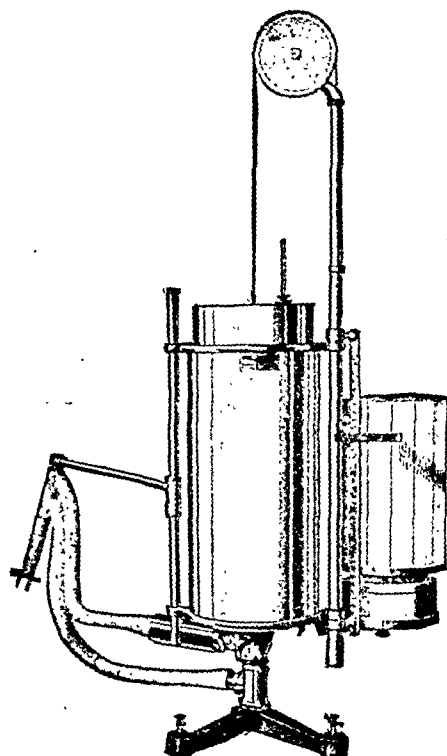
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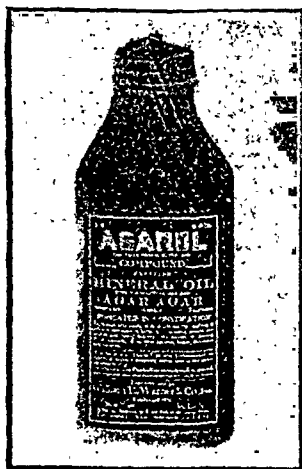
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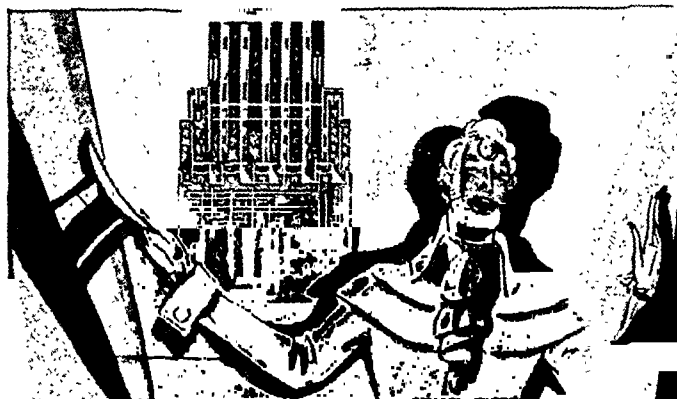
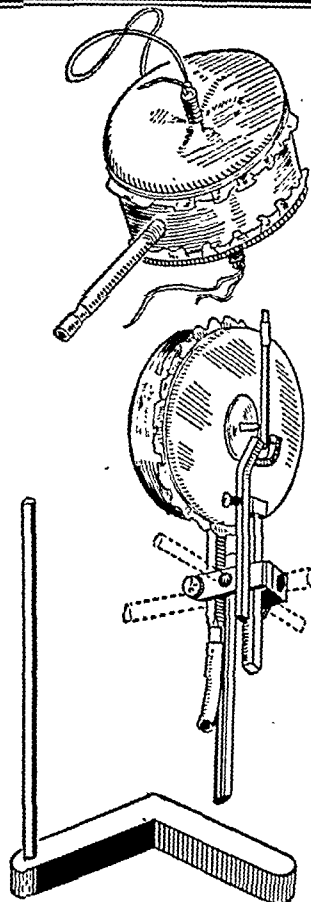
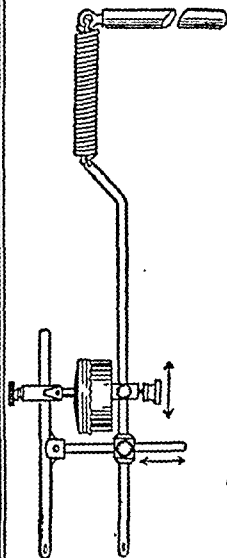
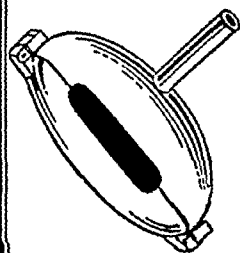
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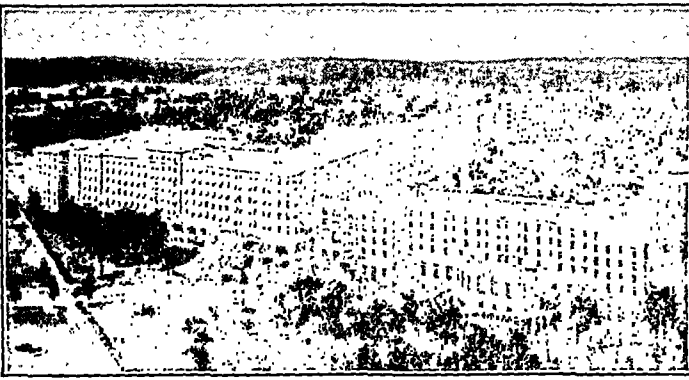
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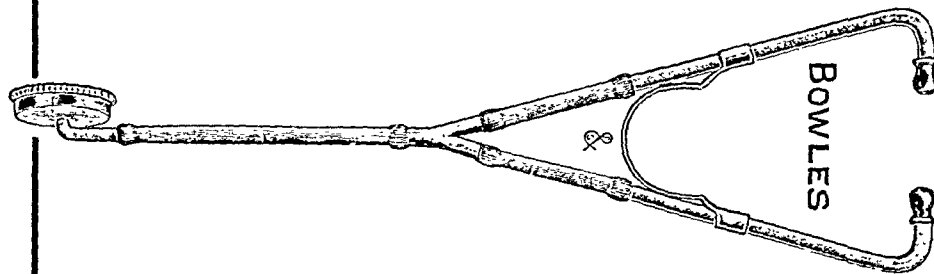
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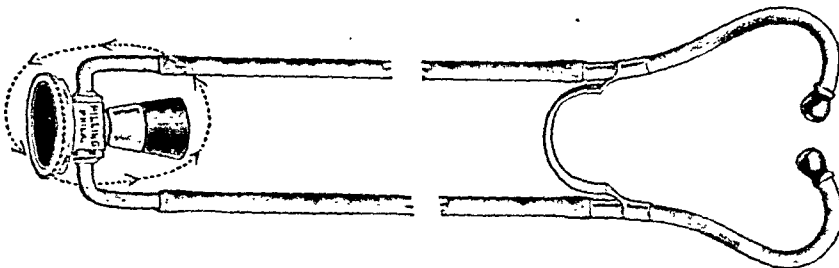
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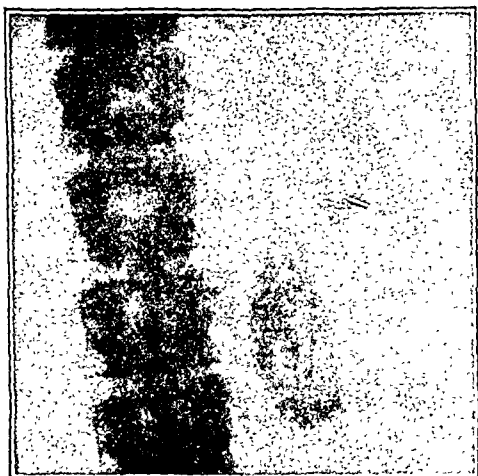
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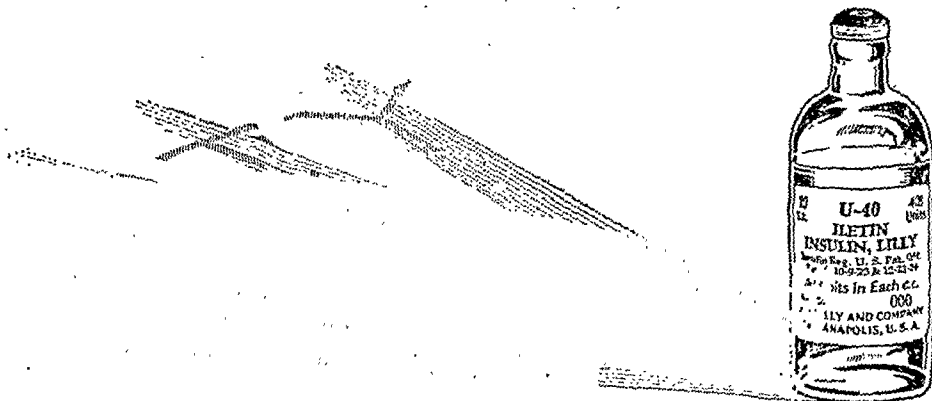
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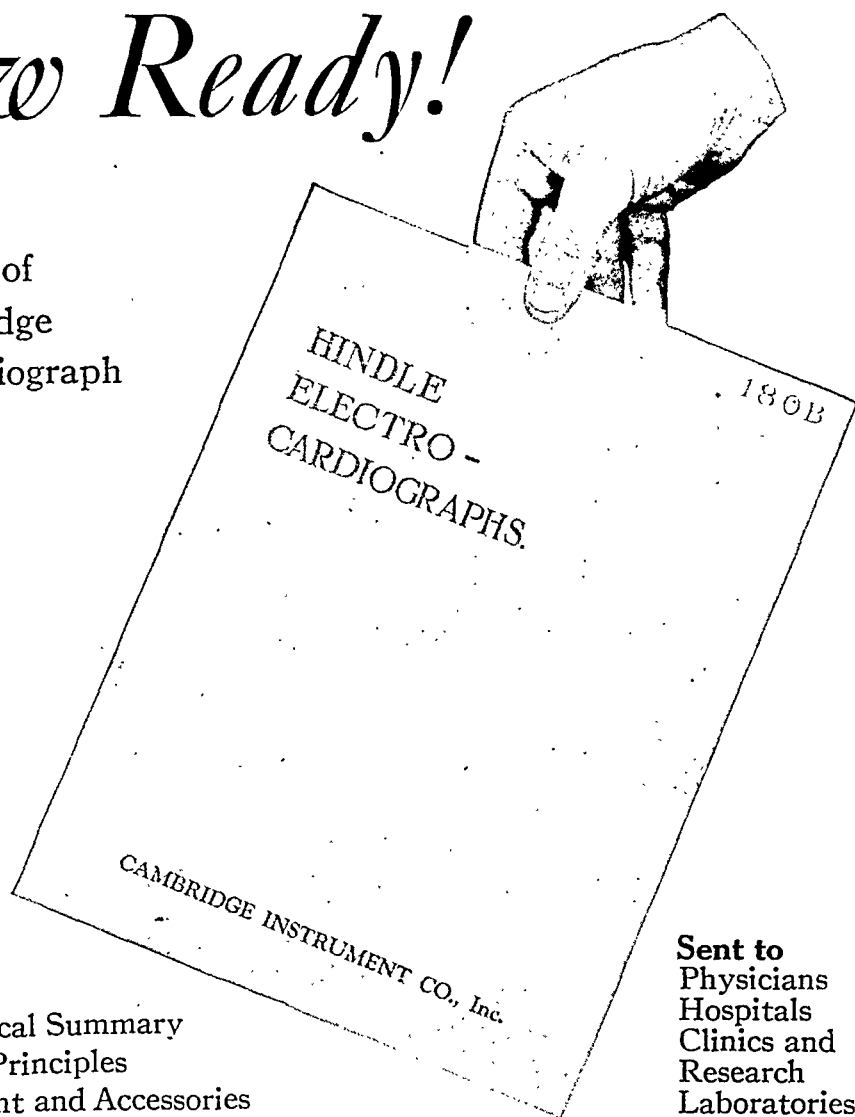
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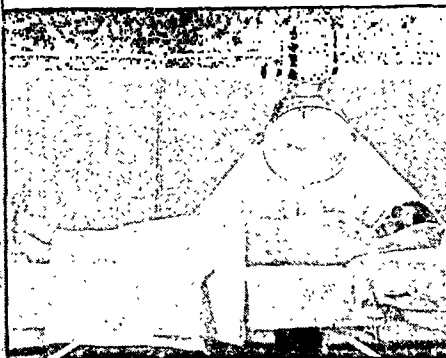
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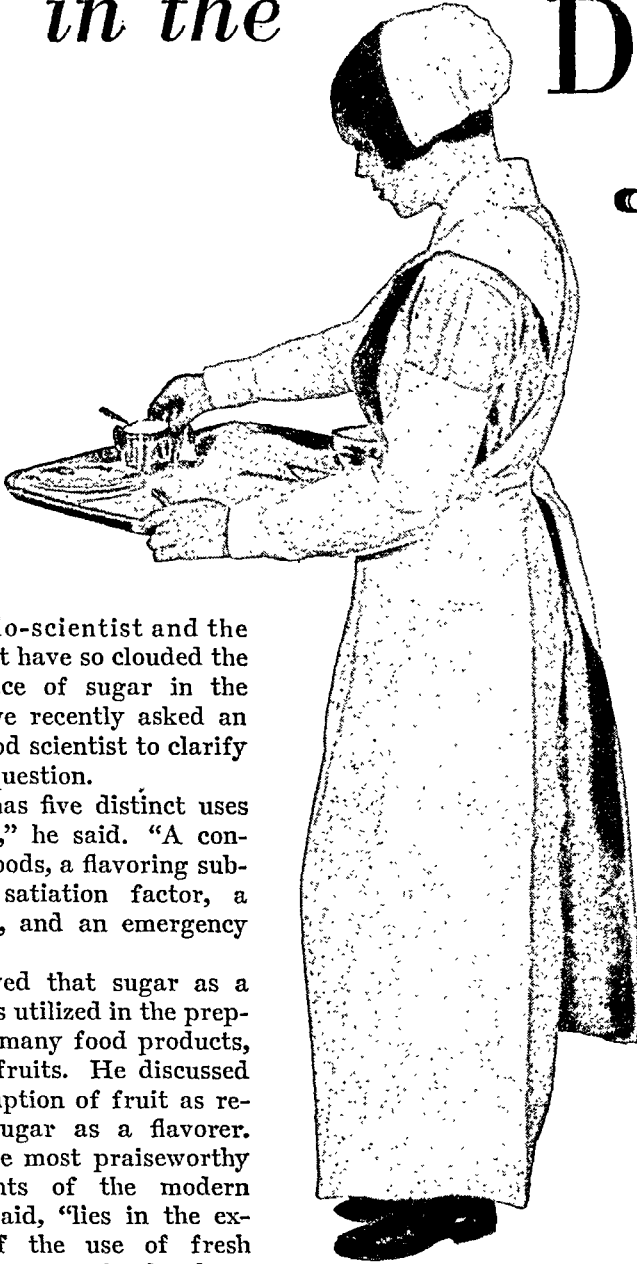
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He showed that sugar as a conserver is utilized in the preparation of many food products, especially fruits. He discussed the consumption of fruit as related to sugar as a flavorer. "One of the most praiseworthy developments of the modern diet," he said, "lies in the expansion of the use of fresh fruits. This expansion has been contingent on the free availability of sugar."

The scientist discussed the use of sugar in desserts, as a satiation factor. "Topping off a meal with a sweet dessert," he said, "gives a sense of satiation. This sense of satiation is an important item in the diet."

"As a staple food," he pointed out, "sugar ranks with starch. The difference in fuel value between starch and sugar per gram of dried material is very slight. Sugar is more rapidly digested than starch; otherwise they are entirely comparable fuels."

He discussed the proportion desired to be contributed by cereals, sugar, fats, oils and

meats. He said, "The place of sugar among the fuel foods depends upon consumers' desires within the general domain of fuel foods. We are a sugar-loving people; therefore, we rate sugar high and consume it freely in many forms."

"The use of sugar as an emergency fuel," he went on to say, "depends upon its rapid resorption. Sucrose is split into d-glucose and d-levulose. The former is absorbed directly; the latter is converted into d-glucose in the act of resorption. The process of resorption is so rapid that sugar appears in the muscles (the fire-box of the body) within a few minutes after ingestion. Practical experience has confirmed experiment in this regard."

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There has been so much dietary misstatement, and so much injury resulting from it, that it is time for medical and scientific authorities to instruct the public to eat enough and to learn the value of sugar for making nearly all healthful foods enjoyable. The Sugar Institute, 129 Front Street, New York City.

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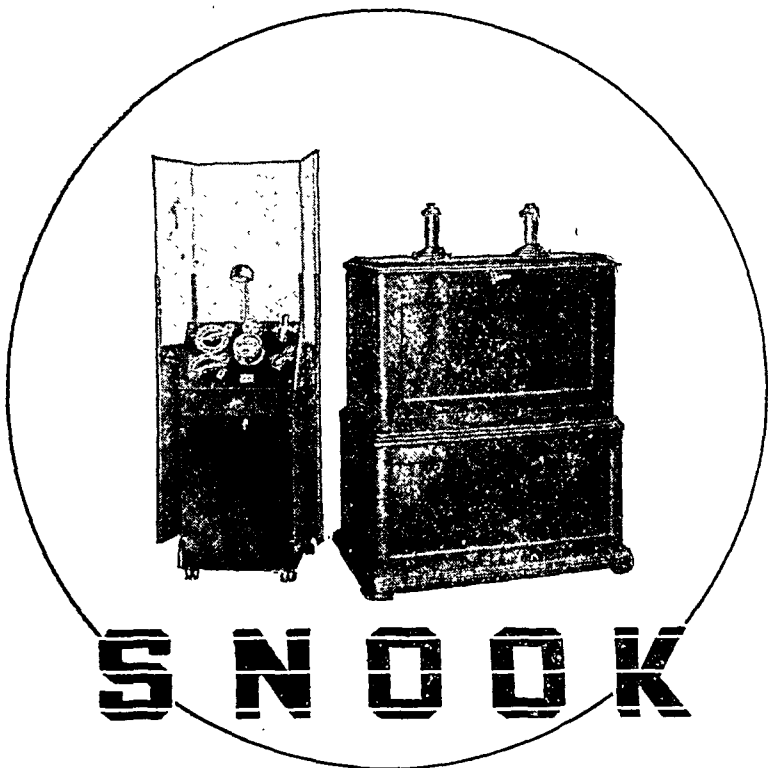
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ORIGINAL ARTICLES.

THE PERSISTENCE OF A MITRAL STENOTIC MURMUR IN
THE PRESENCE OF AURICULAR FIBRILLATION.*

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MACKENZIE¹ seems to have been the first to emphasize the disappearance of the mitral presystolic crescendo murmur with the development of auricular fibrillation, which he, at that time, mistakenly called nodal rhythm. The fact of its disappearance was explained by him as due to the cessation of coördinate auricular systole, a fact which he was also the first to demonstrate in man. Since then, it has come to be accepted as almost axiomatic that auricular fibrillation and a mitral presystolic murmur cannot exist together. It is my purpose in the present communication to show that it is not uncommon to encounter patients with rheumatic mitral disease and fibrillation of the auricles in whom a mitral murmur is clearly heard to continue right up to the first sound of the heart. These cases occur so frequently that it is rare for a month to pass without there being one or more to demonstrate to my students. In a considerable proportion of such cases, this murmur sounds definitely crescendo at its termination in presystole, and is, therefore, identical with that murmur which is regarded as most characteristic of mitral stenosis when the regular sinus rhythm is present. I propose to offer evidence in support of the theory that this apparent paradox is due to an auditory misinterpretation produced by the

* Read before the Association of American Physicians at Washington, D. C., May 1, 1928.

shortening of diastole and the accentuation of the first heart sound. The persistence of such a murmur during fibrillation has lead to considerable confusion and it is my further purpose to attempt to clear this up by an analysis of the phenomena as observed clinically in a large number of cases.

The persistent murmur has been recorded by a number of observers. As is to be expected, Mackenzie himself observed and sought to explain this seemingly inconsistent phenomenon. He wrote: "In the careful examination of a large number of these cases of nodal rhythm we find that the first sound has not the sonorous rumble of the normal first sound, but is represented by a sharp, short snap of very brief duration. Preceding this snap, in a very few cases I have heard a brief crescendo murmur, but a venous tracing showed that there was no auricular systole at the normal time. From this, I suggest that the disputants in the matter have hitherto been confusing two separate conditions. As I have already pointed out, the evidences of auricular systole producing a presystolic murmur are indisputable. While the auricular systole is one cause, it is obvious there must be another cause in these cases of nodal rhythm, and I, therefore, accept the view that a slight regurgitation through the mitral orifice at the beginning of ventricular systole may produce the brief presystolic murmur."

The occurrence of a murmur during the stage of presystole in the presence of auricular fibrillation is a phenomenon which has so arrested my attention during a number of years that every patient presenting it has been subjected to detailed auscultatory investigation. The results of these investigations form the subject of the present discussion.

Two different and distinct murmurs occur with stenosis of the mitral valve. The one is an isolated, short murmur occurring synchronously with contraction of the auricles. It may be soft, blowing and rather indistinct, or, less commonly, it may be rough and rumbling. It usually gives the impression to the ear of being crescendo. This murmur is correctly attributed to the influence of auricular systole. To distinguish it from the murmur next to be described it should properly be called the *auriculosystolic* murmur. The use of this term has the dual advantage of being appropriately descriptive and of avoiding, in part at least, confusion with the more common diastolic murmur which is equally characteristic of mitral stenosis. The *auriculosystolic* murmur is of rather infrequent occurrence.

The second murmur is not limited to presystole, but begins at or before mid-diastole and continues through to end in the first sound of the heart. It is almost always coarse and rumbling and it frequently seems to increase in intensity in presystole so that, to the ear at least, it appears to be clearly crescendo at its ending. This is the murmur which is most commonly present and, as in the case of the

auriculo-systolic murmur, it too, is very commonly called a presystolic murmur. Since this murmur occupies a considerable portion of diastole and is never confined to presystole, it is much better to speak of it as the *diastolic* murmur of mitral stenosis, thus effectively avoiding confusion with the foregoing. The crescent ending of this diastolic murmur is usually attributed to the influence of auricular systole, although this has been denied by a number of investigators.² I shall return to this matter later. These are the murmurs heard when the heart is beating regularly. The common failure to differentiate between them is, I believe, responsible in large measure for the confusion which exists as to the persistence of a presystolic murmur during auricular fibrillation.

In the course of the years during which my investigations have been carried on, there has been opportunity to study a very large number of patients who have presented the combination of mitral stenosis and auricular fibrillation. Never, in my experience, has the isolated, auriculosystolic murmur been heard in these cases. This confirms Lewis,³ who says in discussing the influence of fibrillation on the mitral presystolic murmur, that the murmur is not found in presystole while the remaining portions of diastole are free from it. On the other hand, Josué and Barbier⁴ report one instance of auricular fibrillation in which an isolated, short, crescendo presystolic murmur was heard definitely in the absence of a diastolic rumble. And in 2 of the 4 cases reported by Hart⁵ the murmurs are described as, a short, rough, rumbling murmur preceding the loud first sound; and a first sound, preceded by a thrill and a short, harsh crescendo murmur. It is possible that in exceptional instances such as these we are dealing with a murmur produced by slight regurgitation through an incompletely closed mitral valve, occurring just at the inception of ventricular systole, as believed by Reid. However, as stated, it has never been my fortune to have heard this isolated presystolic murmur, and from both the literature and my own experience I conclude that its occurrence must be quite rare.

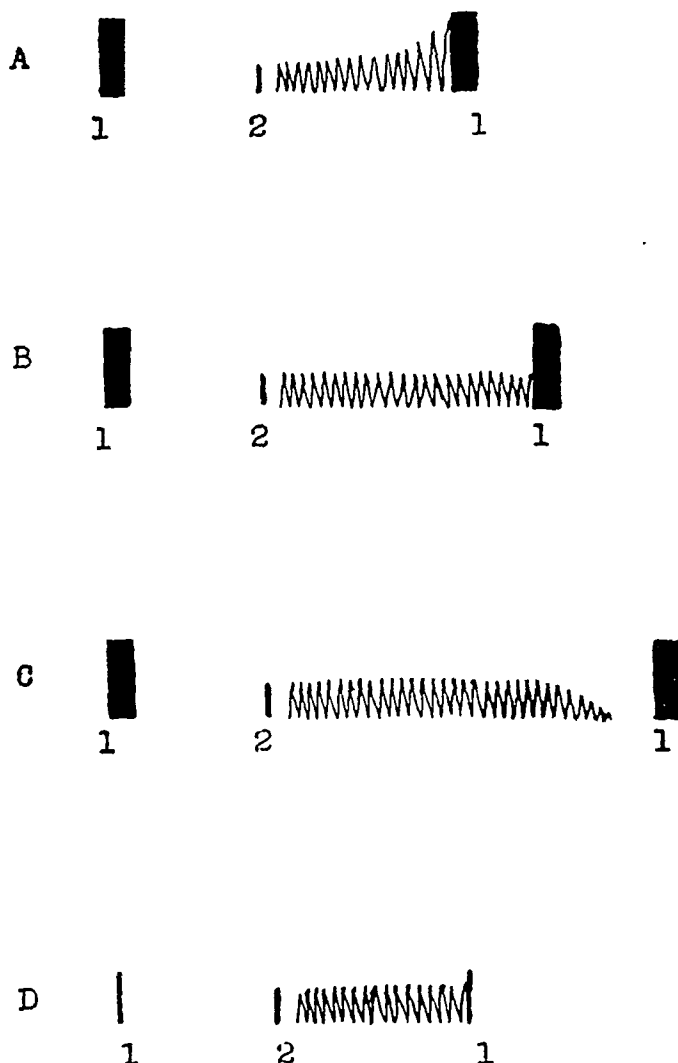
The second type of murmur—the mitral diastolic—which begins at an earlier stage of diastole and then continues through presystole to end in the first heart sound, is the one which may remain after the auricles have passed into fibrillation. Such a murmur is, in a strict sense, presystolic in its termination only. Its persistence has now been observed in more than 40 patients, indicating a much higher incidence than has heretofore been thought to obtain. All of the patients were suffering from rheumatic heart disease and in all the evidences of mitral stenosis were such that this clinical diagnosis could not have been called into question. No patients showing evidences of lesions at other valves have been included. The presence of auricular fibrillation was established by electrocardiograms. Several of the patients who died were proved at autopsy to have had advanced degrees of mitral stenosis with great narrowing of

the orifice. Critical study of this murmur and of its variations as observed in this fairly large group of cases yields the following facts.

The murmur is always of the type usually described as rough, rumbling or purring. It is of low pitch. As already mentioned it invariably starts in diastole at a time definitely earlier than that commonly termed presystole. The murmur rarely seems to be limited to the latter half of diastole. It is always, however, of greater duration than is the brief, isolated auriculosystolic murmur. In the great majority of cases, the murmur fills diastole from the time of its commencement, very shortly after the second sound, right through to the first sound. However long this murmur may be, I have never observed it to become diminuendo in mid-diastole in these patients, as it does fairly often in patients with the regular sinus rhythm. When the first heart sound is short, sharp and much accentuated the impression is given to the ear that the ending of the murmur is reinforced and of crescendo type. This is the case, however, only when the diastolic pause is comparatively brief. The murmur is thus typically developed in all of its characteristics only when the ventricular rate is moderately rapid, usually 100 or more per minute. When the rate lies above 125, diastole becomes so short that the blending of the murmur and the loud, sharp first sound makes the former seem to be quite typically presystolic. Under such circumstances, the murmur may readily be confused with the auriculosystolic murmur as heard in the regularly beating heart. Finally, its auscultatory characteristics in short diastoles as well as in those of moderate length may be compared at will and repeatedly with those in the long diastoles by the simple process of temporarily increasing the heart rate by exercise.

The changes which take place in this murmur when the ventricular rate is markedly slowed following the administration of digitalis, or as the result of rest in bed, suggest the mechanism by which each of its characteristics is produced. Further, since these changes can be studied in one and the same patient we can be sure that we are dealing with the same murmur throughout. The first alteration to be observed is that the duration of the murmur increases as the period of diastole lengthens. Thus it is often found to be of greater length than the total time occupied by diastole at the normal heart rate of 72 per minute. In some patients it is observed to be very much longer than normal diastole. For almost its entire duration it seems to the ear to be of uniformly sustained intensity until shortly before its termination. When diastole is long enough the murmur always stops before the first sound, leaving a period of silence of lesser or greater length. Under these conditions, the ending of the murmur is invariably of more or less rapidly diminishing intensity, so that it dies out rather than stops. This diminuendo termination is as characteristic as is the earlier sustained intensity. These features are illustrated diagrammatically in the accompanying figure.

The fact that the same murmur which fills all of presystole, and perhaps even seems to be crescendo as it ends in the first sound when the heart rate is rapid, can be shown to be long and to cease with a diminuendo ending prior to the first sound when diastole is prolonged, shows that the character of the termination depends largely



Schematic representation of the changes heard in the diastolic murmur of mitral stenosis during fibrillation. 1 indicates the first sound of the heart; 2 indicates the second sound of the heart; A shows the seemingly crescendo ending as heard in shorter diastoles; B shows the absence of the crescendo ending when diastole is somewhat longer; C shows the diminuendo ending and the silence following it in very long diastoles; D shows the absence of crescendo ending when the first sound of the heart is feeble.

upon the rate of the heart, or more specifically upon the duration of diastole. In other words, the termination of the murmur is not dependent upon the mechanism of its production, but rather upon the circumstances under which it ends. Thus, when an early appearing systole cuts the murmur off at a time when it is still of full

intensity, its ending is clearly presystolic in time. Further, when the murmur is loud and rough and the first sound is both sharp and greatly accentuated, then its abrupt termination by this sound gives the impression to the ear that the murmur ends with a crescendo reinforcement. When the first sound occurs after the murmur begins to wane, no crescendo appearance is noted, even though the first sound is unchanged. In cases in which the first sound is poorly developed and feeble, a crescendo appearance is not given to the murmur, however early in its course it is terminated by the sound. And, finally, when the murmur is of rushing or blowing type rather than rough and rumbling, its ending does not appear crescendo even when the first sound is loud and sharp. The seemingly crescendo termination is thus seen to be due to the abrupt interruption of an otherwise long, uniformly sustained coarse murmur by a loud and sharp first sound which falls early because diastole is shortened.

Two patients have been studied over a period of several years, both of whom presented clinically typical rheumatic mitral stenosis. Both were observed for some time with regular sinus rhythm and in both the murmur began early in diastole, was well sustained, and, becoming crescendo in presystole, ended in a loud, sharp first sound. In both, the murmur was very rough. Each of these patients developed auricular fibrillation in the course of time, and with its appearance the murmur in each instance remained unchanged so long as the heart rate was more than 100 per minute, except that in occasional long diastoles the termination lost its apparent crescendo character. Slowing of the heart by digitalis brought out the phenomena which have just been described. Acceleration by exercise then caused the murmur to resume its seemingly crescendo ending. In one of the patients the fibrillation lasted less than twenty-four hours, when the normal rhythm was resumed. The murmur remained unaltered. Subsequently, fixed fibrillation developed, and during it the response of the murmur to slowing of the heart was studied with the results mentioned.

A third patient, who first came under observation shortly after the development of fibrillation and in whom all of the features of the murmur were studied during diastoles of widely varying duration, was given quinidin and her heart resumed a sinus rhythm. During the persistence of the normal rhythm—about ten days—no change in the murmur could be detected if the comparison was made with its appearance in the shorter diastoles during fibrillation. In all of the other patients observed, fixed fibrillation was present throughout the whole period of their study.

The most satisfactory conception of the mechanism by which murmurs are produced is that of the formation of a jet, or the *veine fluide* of Chaveau. This mechanism has been reviewed and amplified recently by Reid.⁶ Narrowing of the mitral orifice yields almost ideal conditions for the production of a rapidly flowing jet of blood as the stream enters the ventricle. When the stenosis is

marked, the jet should occur throughout the greater part of ventricular diastole. In very pronounced stenosis it should persist until the intraventricular pressure begins to be raised to the level of that in the distended auricles by the onset of ventricular systole. Wiggers⁷ says that it is probable that ventricular filling takes place very slowly in the more marked grades of mitral stenosis and continues throughout the entire period of ventricular diastole. He also says that the higher grades of stenosis are always accompanied by diastolic murmurs. Lewis points out that the duration of the murmur depends on the degree of stenosis, the tighter the stenosis the longer the murmur.

The clinical features of the murmur which have been recorded as observed in the presence of fibrillation support this theory of the mechanism of its production. The mechanical and dynamic factors of a tightly constricted mitral orifice, a greatly distended left auricle continually receiving blood under an elevated pressure from the right heart, and a ventricle in which the pressure remains low due to slow and often inadequate filling are such that they must remain essentially unchanged whether the rhythm be regular or the auricles be fibrillating. The only important difference between the two states is the absence during fibrillation of the presystolic auricular contraction. That such a terminal reinforcement of the jet of blood is not necessary for the appearance of what seems to the ear to be a crescendo termination of the murmur is established by its persistence in these cases of fibrillation.

The cause of the crescendo accentuation of the mitral diastolic murmur has been the subject of much argument, and Reid⁸ has recently reopened this subject in a series of papers. Reid, like Mackenzie and others whom he cites, contends that the terminal crescendo portion of this murmur is really not a part of the diastolic murmur but is an entirely separate sound produced by brief regurgitation due to the onset of ventricular systole. According to Reid, this mechanism is capable of causing a murmur which would precede the first sound since it would be due to backflow during that brief period which might be expected to elapse before the stretched mitral curtains were snapped taught. While this may be the mechanism involved in rare cases, I believe that the phenomena may be much more simply explained.

The explanation I have to offer is that the murmur under consideration never, in fact, ends with a crescendo reinforcement in the presence of auricular fibrillation. The apparent crescendo ending is an auditory illusion due to the abrupt termination of the rough murmur by the loud, sharply accentuated first sound, which has a pitch that is not widely different from that of the murmur itself. This explanation is in perfect accord with the observed changes which the murmur undergoes with varying lengths of diastole, and with the fact that it has not been observed to appear crescendo when the first sound is weak, however short the diastole.

Further confirmation of the foregoing explanation is found in the simultaneous phonocardiograms and electrocardiograms obtained by Lewis. In 2 patients (tracings 10 to 14 inclusive, p. 257) his records show that the relation of the termination of the murmur to the first heart sound is entirely dependent upon the duration of the diastole in which it occurs. In each patient the murmur was recorded as merging with the first sound when diastole was brief, and as fading out with a definite diminuendo ending in long diastoles, leaving an interval of silence preceding the first sound.

The rôle of auricular systole in the production of the crescendo ending of the mitral diastolic murmur in the presence of the normal sinus rhythm has been called in question on a number of occasions. While it is not my purpose to discuss this subject in the present communication, I should like to suggest that, in such cases too, the crescendo ending may sometimes also be an auditory illusion. Those who deny its being due to auricular systole have so far failed to recognize the possibility that the crescendo appearance may be an artefact produced in the manner here described. At least as much objection may be raised against the theory that it is caused by early regurgitation of blood from the ventricle as to its being merely an auditory deception. Finally, in closing, it should be mentioned that in some cases in which definite crescendo development of the murmur has been heard phonocardiograms have failed to reveal any evidence of an intensification of the sound.⁹ Lewis' excellent phonocardiograms also show the absence of a true intensification of the murmur in presystole, as revealed by the amplitude of its vibrations. And Lewis, referring to his sound records, states (p. 249) that a conspicuous crescendo appearance of the murmur is present so infrequently in the phonocardiograms that it seems probable that the crescendo quality as imparted to the ear is rarely formed by the murmur alone, but is really made up of a combination of murmur and first sound.

Summary. 1. A murmur occurs in presystole in a considerable number of patients suffering from mitral stenosis and auricular fibrillation.

2. The presystolic murmur thus heard is a continuation of a murmur beginning earlier in diastole. It is suggested that this murmur should be spoken of as the diastolic murmur of mitral stenosis to differentiate it from the true auriculosystolic murmur.

3. The termination of this murmur in some instances seems to be distinctly crescendo.

4. The crescendo ending is explained as an auditory illusion produced by the merging of the rough murmur with the very loud, sharp first sound. It is not heard when the first sound is feeble, or when the murmur is soft and blowing.

5. The murmur is much prolonged and has a diminuendo ending when heard during long diastoles.

6. It is a valuable diagnostic and prognostic sign since it is

probably found only in the presence of a markedly stenosed mitral orifice.

7. A murmur limited entirely to presystole, with the remainder of diastole free from sound, has not been heard in the presence of auricular fibrillation in a large group of patients. This murmur heard only in the regularly beating heart, should be termed the auriculosystolic murmur.

NOTE.—While this paper was in press an article appeared by Wilhelm Dressler, (*Wiener klinische Wochenschrift*, 1928, 41, 1245) in which the author contends that the presystolic murmur is produced in regular hearts by auricular contraction. He contends also that the crescendo quality of the murmur is not a characteristic of the murmur itself but depends upon an auditory deception (*Gehörstuschung*) produced by its abrupt termination in the loud first sound.

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SYMPATHECTOMY IN THE TREATMENT OF ANGINA PECTORIS.

COMPARISON OF RESULTS WITH THOSE FROM PARAVERTEBRAL ALCOHOL INJECTION.

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AND

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Introduction. That painful stimuli arising in or near the heart may be modified by destructive interruption of pathways connecting with the central nervous system, has been clearly demonstrated. The treatment of angina pectoris by sympathectomy, suggested by Franois Franck¹ in 1899, and first carried out by Jonnesco² in 1916,

was given impetus in this country by Coffey and Brown³ in 1923, who reported successful results from operations upon the left superior cervical ganglion only, rather than from the bilateral removal of the whole cervical sympathetic chain, including the first thoracic ganglia, as advocated by Jonnesco.⁴ This substitution of a limited for a rather extensive operation led to an increase in the number of cases operated upon, and corresponded to a renewal of interest in the subject abroad. Consequently many cases of angina pectoris treated by operation, for the most part on the cervico-thoracic sympathetic chain, have appeared in the literature, and have been summarized by Fontaine,⁵ and more recently by Cutler.^{6,7} In 1926, another development came when Swetlow⁸ reported relief of pain by blocking the communications of this chain with the central nervous system by means of paravertebral injection of alcohol.

Although it may be conceded that the pain of angina pectoris can at times be relieved to a greater or less degree by these alternative procedures, operation or alcohol block, do these methods of treatment constitute good therapeutics, and if so, to what extent? This question may be answered only in part by the operative mortality and by the degree of relief immediately obtained. Further desirable criteria are the permanence of relief and in particular, the effect of operation on the duration of life, either through the interruption of the sympathetic innervation, or through the abolition of the symptom pain. Since interruption of the sensory stimuli probably does not alter the underlying pathology of angina pectoris, it has been suggested that the relief of the paroxysmal pain is harmful because thereby a warning symptom useful to the individual is done away with. On the other hand, it may be argued either that a reflex vascular spasm or a condition of shock excited by these stimuli is a cause of sudden death, or that the heart might be better for more exercise than the recurrent pain allows it. Such points may only be decided by following the clinical course of patients after treatment. Unfortunately, most of the reported cases have been published very shortly after operation. It is extraordinarily difficult to evaluate the indirect effects of operation in a symptom complex like angina pectoris, with a variable underlying pathology, a tendency to sudden accidents, and to spontaneous improvement. Under these circumstances, the place of radical therapeutic measures can only be gradually established through the accumulation of the late results of treatment.

Eight cases of angina pectoris were operated upon at the Massachusetts General Hospital between August, 1923, and December, 1926. Since the subject as a whole has been so admirably reviewed by Cutler,^{6,7} the purpose of this paper is merely to present our own results of treatment, and the relative effects of operations which varied in extensiveness. Since February, 1927, paravertebral injec-

tion of 85 per cent alcohol, according to the method of Swetlow⁸ has been used instead of operation. These injections were made by J. C. White and by W. J. Mixter,^{9,10} and have been previously reported. An opportunity is thereby given to compare the effectiveness of operation and of paravertebral alcohol injection.

One important aspect of the subject is the selection of cases. While our impression of the type of cases suitable for these more radical forms of treatment will be given after a discussion of the results obtained, a few general considerations properly appear at this point. In the first place, there should be no question as to the diagnosis of angina pectoris, as distinguished from other forms of cardiac pain like that of coronary thrombosis or of effort syndrome. In any new treatment, the value of which is debatable, accuracy in diagnosis is peculiarly desirable. In some instances cited in the literature, operation has been performed upon patients in whom the diagnosis appears doubtful. Even the description of Jonnesco's² first case, cured for seven years, suggests paroxysmal tachycardia rather than angina pectoris. It should be further recognized that even if true angina exists, it is not incompatible with a considerable duration of life, or with attaining an age well beyond the average. By limitation of activity and particularly by avoiding conditions known to bring on attacks, patients may live for many years in relative comfort. In other cases, in spite of such care, and the relief obtainable through the use of the nitrites, the frequency and severity of attacks even during rest may be such that the suffering and disability are intolerable. Therefore, broad familiarity with cardiac conditions is necessary both for the diagnosis of angina pectoris and for the selection of cases for treatment by methods which still must be considered somewhat experimental. The occurrence of severe continuous pain due to coronary thrombosis is a contraindication to operative treatment, as is congestive failure, a development, moreover, ordinarily associated with the cessation of anginal attacks.

Since the extent of the removal of the cervicothoracic sympathetic chain varied in our cases, some anatomic discussion is necessary to correlate the clinical results secured with the degree of interruption of known pathways of conduction to and from the heart. The cervicothoracic sympathetic chain is principally efferent in function. It communicates with the central nervous system only through the rami communicantes of the thoracic nerves. Ransom¹¹ states that afferent impulses are carried from the plexus surrounding the heart, aorta, and coronary vessels to the spinal cord along the cardiac branches of the middle and inferior cervical sympathetic ganglia, the sympathetic trunk, white rami, and upper three or four thoracic nerves. The cervical sympathetic trunk above the middle ganglion, the superior cervical ganglion, and the superior cardiac nerve conduct efferent impulses only. The chief area of referred pain in angina pectoris is so clearly that of the cutaneous distribution of the

upper thoracic nerves that any conduction of painful sensations to the brain through the vagus must be of minor importance. We have had no experience with section, as recommended by Wenckebach,¹² of afferent vagus fibers, believed to form in man a separate depressor nerve, and carried out by certain surgeons, notably Eppinger and Hofer.¹³ The function of this nerve in relation to angina pectoris as well as the chance of recognizing it at operation seem to us so doubtful as to make it an unpromising line of attack. On physiologic grounds, therefore, there are two points at which an effective block of sensory impulses passing through the sympathetic nervous system from the heart can be carried out. One is in the region of the inferior cervical and first thoracic ganglia, and is most simply accomplished by removal of these structures. The second is by interruption of the rami communicantes of the upper thoracic nerves. Division of the sympathetic trunk above the middle ganglion or of the superior cardiac branch, or removal of the superior cervical ganglion which interrupts both these structures, while breaking motor pathways to the heart, does not divide afferent fibers going to the spinal cord.

The operations, limited to the left side, carried out in the present series of cases were: (1) Removal of the superior cervical ganglion as recommended by Brown and Coffey;¹⁴ (2) removal of the superior ganglion and sympathetic chain down to the level of the first thoracic ganglion; (3) removal of the inferior cervical and first thoracic ganglia, which form the stellate ganglion. Removal of the whole cervical chain including the first thoracic ganglion, the Jonnesco procedure, was not carried out in one stage in any case. The cases treated by operation⁸ represent a small proportion of patients with angina pectoris (about 300) seen and followed during slightly over three years, and are presented herewith.

Case Reports. CASE I.—Male, aged forty-nine years, porter, entered the Massachusetts General Hospital on May 15, 1923, with the diagnosis of *syphilitic heart disease, aortitis, aortic regurgitation and angina pectoris*. The first attack of anginal pain occurred eighteen months before, and for thirteen months the attacks had been of increasing frequency. For three months he had been unable to work at all. For two months he had been treated in the out-patient department on account of this pain and a strongly positive Wassermann reaction with mercury and iodids, without benefit to the anginal attacks. The pain came on with exertion and sometimes after eating. It was usually in the region of the left second, third, fourth and fifth ribs, from the sternum to the anterior axillary line, agonizing and oppressive in character, sometimes radiating to the region of the left scapula, but not to the arm.

Examination showed the heart slightly enlarged to percussion and a to-and-fro murmur over the aortic area, with a water-hammer pulse. By Roentgen ray the aorta was a little prominent both to the right and left. The blood pressure was 112 systolic and 50 diastolic. The electrocardiogram showed a normal rhythm at a rate of 80. There was no evidence of congestive failure.

During rest in bed in the hospital he still had attacks of anginal pain, chiefly following meals, relieved by nitroglycerin. He was discharged in ten days, without essential benefit. He then remained quietly at home, but the attacks increased in frequency, so that he took 400 nitroglycerin tablets in three weeks. The attacks began slowly and could be aborted by nitroglycerin, but frequently occurred during complete rest.

He was readmitted for sympathectomy on August 14, 1923. Operation was performed on August 20 under ether anesthesia. The sympathetic cord on the left was removed from the inferior end of the superior ganglion to the superior end of the inferior ganglion. No middle ganglion could be recognized.

He made a good postoperative recovery. Horner's syndrome, narrowing of the palpebral fissure, with contraction of the pupil, occurred on the left. The attacks were relieved for three days, and then gradually recurred. The character of the pain was slightly modified, being located more definitely at the third left costochondral joint and was less agonizing in character.

After discharge on September 3, the attacks gradually increased in severity and in frequency up to thirty a day. The pain remained more definitely limited to the precordia. On October 18 he was readmitted for further operation.

Four days later the superior cervical ganglion was removed under ether anesthesia. Again the attacks ceased for two days, and gradually returned. After discharge they were more frequent than ever, occurring at all times of day or night, but still immediately relieved by nitroglycerin. The location, character and severity of the pain was not further modified by this second operation. He felt, however, that he had been improved and readily accepted the suggestion of further surgical treatment.

On November 24 the left inferior cervical and the first thoracic ganglia were removed under ether anesthesia. The operation proved somewhat difficult on account of adhesions from the previous operations, and from lack of the sympathetic trunk as a guide. The inferior cervical ganglion was found just internal to the vertebral artery, and continuous with the first dorsal ganglion which was behind and below the vessel. These structures were removed without appreciable effect on the patient.

Following operation, his general condition was satisfactory, but five hours later, during a vomiting attack, he stiffened convulsively, became cyanotic, and died within two or three minutes. There was no autopsy.

Comment. The operations in this case were limited in extent, in the hope of verifying what part of the sympathetic was most concerned in the transmission of impulses associated with angina pectoris. The sympathetic cord was removed first, since it was felt that thereby more afferent pathways would be severed than by the removal of the superior ganglion. While after this operation there was no theoretical reason why excision of the isolated ganglion should lead to further benefit, it was done as a test procedure. It produced no further observable effect. The effect of removal of the inferior cervical and first thoracic ganglia, from which much was hoped, could not be observed. The death of the patient seemed to be of cardiac nature. Subsequent cases were closely watched for forty-eight hours after operation, in order to give inhalation of amyl nitrite on the first sign of cardiac distress. This patient is classed as essentially unrelieved by his first two operations.

CASE II.—Male, aged fifty years, laborer, entered the hospital October 25, 1923, after two weeks' observation in the cardiac clinic. About three months previously he began to have epigastric distress, radiating to the front of the left chest, and occasionally down the left arm. For two months it has been intense, and it left the patient weak and shaken. The attacks followed slight exertion, and occurred several times while at rest during the night. Nitroglycerin, at first effective, now failed to relieve the pain. He had been unable to work.

Examination was essentially negative aside from slight cardiac enlargement with evidence of peripheral arteriosclerosis. Roentgen ray showed the heart shadow enlarged to the left, the apex unusually blunt; there was no abnormality in size and shape of the aortic shadow. The electrocardiogram showed a normal rhythm, rate 70. The Wassermann reaction was negative; the blood pressure was 180 systolic and 90 diastolic. A diagnosis of *hypertensive and arteriosclerotic heart disease with angina pectoris* was made.

On November 7, 1923, removal of the left cervical sympathetic chain was carried out under ether anesthesia. The lower two-thirds of the superior ganglion, the sympathetic trunk, the middle ganglion, and the inferior cervical ganglion lying beside the vertebral artery were excised. The first thoracic ganglion was exposed but not removed.

Following operation, the patient had a cough and temperature reaction apparently due to a mild grade of bronchopneumonia. He had no more attacks of angina, but had occasionally a "warm" sensation over the precordia. Horner's syndrome occurred on the left, but there was no observable difference in the superficial circulation of the face.

On February 15, 1924, he reported himself symptomatically very much improved. He had had no pain at all, was able to walk for half an hour, and to carry coal up from the cellar. On exertion he sometimes had dyspnea and a sense of warmth at the second and third interspaces above the precordia.

On December 17, 1925, his family stated that he had returned to Poland in July, where he was working on a farm. Previously he had worked nine hours a day handling wet leather, and was able to walk a mile and a half to and from work. During this time he had some pain in his chest when he walked fast or overexerted himself, but he needed no medication.

On January 13, 1927, a letter from Poland stated that he was working on a farm, was very well and had no complaints.

At Christmas time, 1927; he continued to feel well except for some ill-defined leg-ache. There was little or no angina pectoris and no discomfort from the operation (cervical sympathectomy) that had been done over four years previously.

On August 11, 1928, the son reported that his father was well as far as his heart was concerned but complained of rheumatic pains in his legs. He was working on the farm in Poland. This was nearly five years since the operation.

Comment. The degree of benefit obtained for nearly five years in this case was very gratifying. While not entirely cured symptomatically, he was enabled to do manual labor, and was entirely satisfied with the result. We should class him as at least 90 per cent relieved.

CASE III.—Male, aged fifty-three years, machine operator, entered the hospital on November 19, 1923. For two years he had had attacks of typical anginal pain, occurring over the precordia with radiation down the left arm. The attacks were associated with exertion, and occurred with

increasing frequency up to three or four times a day, causing him to give up work. His Wassermann reaction was strongly positive, and he had received a five months' course of antiluetic treatment, consisting of mercury, potassium iodid and neocarsphenamin, without benefit.

Examination showed his heart slightly enlarged to the left. A to-and-fro murmur loudest over the aortic area was heard. Roentgen ray confirmed the cardiac enlargement, and showed prominence of the aorta to the right and to the left. He was somewhat dyspneic, but showed no other evidence of congestive failure. The blood pressure was 146 systolic and 44 diastolic.

After a year's observation and treatment in the cardiac clinic of the outpatient department, he was sent in for sympathectomy, on account of his disability and lack of improvement, with a diagnosis of *aortitis (luetic), aortic insufficiency and angina pectoris*.

On November 21, 1923, the left sympathetic chain was removed to the level of the subclavian artery, including the superior ganglion, the sympathetic trunk, and the inferior ganglion. During convalescence he had no anginal attacks, and was discharged with the wound healed on the seventh day. Horner's syndrome was produced. After returning home the attacks recurred, and became more frequent and severe than before the operation. He died a cardiac death on July 6, 1924. There was no autopsy.

Comment. This patient showed temporary inhibition of attacks while in the hospital, perhaps as a result of anesthesia and rest, a phenomenon observed in other cases, and apparently having no significance with relation to permanence of relief. The operation, however, must be classed as completely ineffective in relieving the anginal pain.

CASE IV.—A male steward, aged thirty-seven years, came to the hospital on January 14, 1924, complaining of attacks of distress over the lower precordium of three years' duration. These attacks were brought on by exertion, and had a tendency to occur after meals, but also often awakened him at night. He would attempt to relieve them by standing up and taking long breaths, with an effort to belch. Twenty months previously on account of increase in frequency and severity, he consulted a physician who had his blood examined, said he had syphilis, and treated him by medication with some improvement until six months before admission. Then the pain became more severe and was brought on by very slight exertion. For the last three weeks he had been unable to work at all. The pain was most marked at the second interspace on the left and sometimes lasted as long as an hour, but was usually much shorter in duration.

Examination showed a thin, pale man, with a slow regular pulse. The heart was not enlarged to percussion. There was a roughening of the first sound at the apex, and a soft blowing diastolic murmur loudest over the aortic area. Blood pressure was 140 systolic and 50 diastolic. The Wassermann test was strongly positive. Roentgen ray showed some general enlargement of the heart but no increase in the supracardiac shadow. There was no evidence of congestive failure. The diagnosis was *luetic heart disease, with aortic regurgitation and angina pectoris*.

He remained on the medical wards for six weeks, having frequent attacks of substernal pain while in bed, especially at night, relieved by nitroglycerin. Mild antiluetic treatment seemed to increase rather than to relieve the pain. Accordingly sympathectomy was advised and carried out on March 3.

He became cyanotic under ether anesthesia although the quality of his pulse was good. The main sympathetic trunk was exposed and divided

1 inch above the inferior thyroid artery and the wound closed. After removal of the ether, the patient's color did not improve. He began to cough up pinkish froth, and died from pulmonary edema within twenty minutes, in spite of venesection and the administration of adrenalin, digifolin and atropin.

Comment. Death in this case was due to the effect of anesthesia on an incompetent heart. Section of the sympathetic cord undoubtedly had no effect on the outcome, which might easily have followed any minor operative procedure.

In view of the increasing number of cases in which good results were reported from removal of the left superior cervical ganglion alone, it was now decided to limit the operation to removal of this structure at a first stage, and if further operation seemed indicated to remove the inferior cervical and first thoracic ganglia. While ether had been chosen as an anesthetic, believing that through its similarity to alcohol and its vasodilator effect it would not provoke anginal crises, limiting operation to the superior ganglion had the advantage that it could readily be carried out under local anesthesia.

CASE V.—A married Italian woman, aged twenty years, entered the hospital May 2, 1923, complaining of pain in the left arm and chest, shortness of breath and weakness. When she was six years of age she was ill for four months with rheumatic fever. During the next three or four years she had rheumatic attacks. From the age of ten until two years before admission she was well. Then she began to have pain in the left arm, dyspnea on exertion, palpitation and slight unproductive cough. She was in bed two months. Between September, 1921, and the date of entry she had three attacks of "cold" and "sore throat," with intensification of her symptoms. The pain in her left arm and left chest caused her to stop work.

Examination showed a well-developed and well-nourished young woman whose body was shaken by her cardiac pulsations. The heart was enlarged downward and to the left. There was a thrill over the aortic area, accompanied by a harsh systolic murmur. A softer diastolic murmur was heard all over the precordia. The blood pressure was 165 systolic and close to zero diastolic. There was no cyanosis. By Roentgen ray the heart was very much enlarged in all diameters. Electrocardiogram showed normal rhythm, rate 95, marked left axis deviation (index, + 42) and inverted T wave in Lead II. The diagnosis was *rheumatic heart disease, with aortic regurgitation and stenosis and mitral stenosis*.

She reentered January 10, 1924, and remained for three months in the hospital. The attacks of pain were her chief complaint. This pain was sharp, knife-like, occurring over the precordia, and variably transmitted to the left back, axilla and arm. Examination was essentially the same as at the previous entry. There was no evidence of congestive failure. The pain was found to be associated with attacks of tachycardia. Quinidin was given without effect. Nitroglycerin relieved the pain.

Two years later, January 28, 1926, she came to the hospital, having been followed in the cardiac clinic. During this period she had done unexpectedly well, no congestive failure having occurred. The attacks of pain, however, had persisted and become more frequent. They were regularly relieved by nitroglycerin, of which she used nearly 200 tablets in a week and a half. Examination was essentially as before. It had become increasingly evident that the attacks of pain, at first attributed to paroxysmal tachycardia, were actually due to angina pectoris.

Since she was almost entirely incapacitated by the frequent attacks of pain, and had not otherwise lost ground to the extent expected, sympathectomy was thought advisable.

On February 2, 1926, the left superior cervical ganglion was removed under local anesthesia without incident. She was discharged twelve days later without having had any anginal attacks. The operation produced hyperesthesia of the side of the neck and face.

On April 1, 1926, her sister reported that following an attack of influenza she had had a recurrence of anginal pain, relieved by nitroglycerin.

On April 16, 1926, she was seen in the cardiac clinic. About one month before she had had an attack of respiratory infection during convalescence from which she began again to have typical angina pectoris always relieved by nitroglycerin. The attacks, however, were less frequent than before operation, requiring about two or three tablets daily.

In March, 1927, she developed bronchopneumonia at home and died after three or four days from the effects of the pneumonia itself. Prior to the infection she had been much improved as far as her heart and angina pectoris were concerned. There was no postmortem examination.

Comment. This case has been reported in detail.¹⁵ While at first definitely benefited by operation, her attacks soon recurred. The period of relief seems too long to be attributed to the effect of anesthesia, and to the immediate psychologic effect of operation, and seems reasonably due to the sympathectomy, particularly since the angina pectoris when it did recur was much less severe than before operation. Ultimately her attacks of pain became infrequent and mild. No further surgical interference was carried out because of the patient's serious rheumatic heart disease, her respiratory infections, her dislike of further surgery and her gradual improvement. We would class her as 50 per cent relieved, for a period of one year up to her death from pneumonia.

CASE VI.—A male laborer, aged fifty years, entered the hospital on May 18, 1925, complaining of pain in the left chest. Two months previously while working in a brickyard, he had a brief severe attack of pain over the precordium, which radiated to the back and down both arms. Three weeks before admission he was forced to give up work on account of the severity and frequency of similar attacks.

Examination revealed a vigorous looking muscular man. The heart showed a systolic murmur at the apex, but was not apparently enlarged; the supracardiac dullness seemed increased. His blood pressure was 140 systolic and 80 diastolic. The Wassermann test was strongly positive. Roentgen ray showed the heart shadow to be definitely enlarged, the supracardiac dullness increased, although in the oblique view the aorta did not appear to be enlarged. The appearance of the aorta was not characteristic of lues. Electrocardiogram showed normal rhythm, rate 65, left axis deviation.

In the hospital he developed a subdeltoid bursitis and was discharged June 4, 1925.

In the out-patient department he was treated with iodobismuthate of quinin, receiving 15 injections up to September 28, 1925. The attacks of angina pectoris nevertheless persisted and followed exertion, eating and sudden excitement. Nitroglycerin relieved the pain. He tried working for a few days, but had ten to fifteen attacks of pain a day, and was forced to keep quiet at home, where he still had four or five attacks a day. There had been no appreciable benefit from the antiluetic treatment.

On November 2, 1925, he was readmitted to the hospital. The physical examination was essentially the same as at the first entry. The diagnosis was *angina pectoris, tertiary syphilis*.

On November 6, the left superior cervical ganglion was removed under novocain, which had to be supplemented by ether. Until his discharge two weeks later, he was much improved, having, however, occasional mild attacks of pain which did not require nitroglycerin. Following operation, he had pain in the left side of the face on eating, and pain in the left shoulder, which appeared to be due to an intensification of his previous subdeltoid bursitis, but may have been dependent on postoperative hyperesthesia. Horner's syndrome was produced.

Following discharge, the attacks recurred in their previous frequency and severity. The pain in his shoulder and face was extremely troublesome. He was still completely incapacitated. During the interval, he had 8 injections of neosarsphenamin.

On February 1, 1926, he reentered for further operation which was done twelve days later. The aorta was now found enlarged by Roentgen ray in the oblique view and the findings were more characteristic of syphilitic aortitis. On February 12, 1926, under ether anesthesia the sympathetic trunk was picked up on the left where it formed a loop around the inferior thyroid artery, and followed downward, exposing two ganglia, the lower of which, about 1 by 1.75 cm. in size, lay behind the subclavian artery below the origin of the vertebral artery. These ganglia were identified as the inferior cervical and first thoracic ganglia, and were completely removed. During the operation a small opening was made in the thoracic duct.

On the day following operation, anginal attacks occurred, and persisted irregularly through convalescence, once or twice daily, usually waking him from sleep. The pain was precordial, radiating to the left arm, hand, shoulder and scapular region, and also to the left occiput and parotid region. It was relieved by nitroglycerin. The wound healed promptly in spite of injury to the thoracic duct. During convalescence the blood pressure was essentially equal in both arms.

Following operation he reported regularly to the cardiac clinic. The anginal pain occurred as before, and hyperesthesia and pain in his shoulder and also pain in the region of the left lower jaw were extremely troublesome. Between March 25 and May 13, he received 8 injections of neosarsphenamin.

On May 20, 1926, he was not doing well. The pain was substernal, with radiation to both arms.

On June 16, he continued to have attacks of substernal pain. He was unable to work and took several nitroglycerin tablets daily.

On July 8, he was considerably improved; he used about two nitroglycerin tablets daily, and wanted to try some light work.

On August 5, he was getting on fairly well, working nine hours a day loading brick. He still had some angina pectoris, and took two tablets of nitroglycerin daily.

On November 18, 1926, he was feeling better, working three or four days a week handling bricks.

On March 24, 1927, he had been laid off from work since Christmas because of slack business. He felt much better on the whole. There were still attacks of pain, starting midsternally, and radiating down the right arm, usually after eating. He took four to six tablets of nitroglycerin a week. His left hand had been cold since operation. The pain in the left jaw was still present on beginning to eat, but was better. The pain in the left arm and shoulder was all gone. He did not sweat on the left side of the face or in the left arm. He had no disability with his arms on working. The pain in the precordia was less frequent and less severe. When it came it radiated to his right arm and somewhat to the left side of the neck. On examination the left arm and hand were colder than the right.

On February 2, 1928, he reported again. He had worked at intervals at bricklaying. He used two nitroglycerin tablets a day when working, one a week when not. Examination was as previously, fluoroscopy showing a slight aortic dilatation, and slight cardiac enlargement. Horner's syndrome continued.

On May 14, 1928, further antiluetic treatment was advised. There was no change in his symptoms or physical examination from those noted in February, 1928.

On August 16, he was still at work in the brickyard, taking two nitroglycerin tablets daily.

Comment. This case was undoubtedly benefited by the treatment. Whether the improvement should be attributed to operation or to antiluetic treatment is doubtful. We are inclined to believe that the operation had a greater effect than the drug therapy although it certainly was only partially successful.

Pain in the shoulder and jaw in this case was extremely troublesome following operation. However, it eventually disappeared. It is of interest in connection with ischemic conditions of the extremities that the later effect of removal of the stellate ganglion was vasoconstriction rather than vasodilatation. We should class this case as 60 per cent improved.

CASE VII.—A garage owner, aged fifty-nine years, was referred to us in consultation in May, 1926, by Dr. W. A. Putnam of Cambridge, for substernal distress of twelve years' duration, at first only with heavy work or lifting, but then brought on by the least exertion. The pain was substernal and precordial, radiating to the left shoulder, the left arm and left back, extending to the throat somewhat, but not to the face or jaw. The pain was brought on by walking or excitement, but not by meals. It was always relieved by nitroglycerin. Since April he had been unable to work, and the attacks were growing progressively more severe, and were brought on more easily. His past history was not remarkable.

In October, 1926, he was seen again and was no better and operation was thought advisable.

Examination showed a man somewhat overweight, but appearing in good health. His heart was regular in action, and negative to auscultation and percussion. His blood pressure was 135 systolic and 90 diastolic; the urine and Wassermann tests were negative. The diagnosis was *arteriosclerotic heart disease, angina pectoris*.

On October 18, 1926, the left superior cervical sympathetic ganglion was removed under local anesthesia without incident. Horner's syndrome was produced. During the same morning he had an anginal attack, and others occurred on the fifth, sixth and seventh days. The pain was located somewhat more externally, nearer the axilla, but was similar in severity. He also complained of pain in the region of the left jaw, on beginning to eat. He was discharged on the seventh day.

On November 3, 1926, the attacks were the same as before operation in frequency and severity.

On December 9, 1926, he died after an attack of pain lasting twelve hours, believed to be due to coronary thrombosis. There was no autopsy.

Comment. Operation was totally ineffective in this case. It is very improbable that it was in any way responsible for the coronary thrombosis which occurred seven weeks later.

CASE VIII.—A traveling salesman, aged fifty-nine years, was referred to us by Dr. W. A. Putman, December 8, 1926. Six months before he had begun to have slight substernal distress, which was benefited by a month's vacation. On return to work, which involved the carrying of heavy sample cases, the pain became much worse, so that he had done nothing for two months, and during the last two weeks he had been in bed. The attacks ordinarily came on with exertion, but he had had two or three daily while in bed. The pain was relieved by nitroglycerin, of which he was taking 100 tablets a week, and was located under the lower end of the sternum, in the median line, extending outward on both sides equally, and upward to the sternal notch. It was also felt in the left wrist. His health was otherwise good, and his past history without significance; there had been no venereal disease.

Examination showed a florid man, weighing about 215 pounds. His pulse was regular, his heart negative to auscultation and percussion, except for slight cardiac enlargement. Blood pressure was 155 systolic and 90 diastolic. The urine was normal. A *diagnosis of angina pectoris* was made.

On December 13, 1926, his left superior cervical ganglion was removed under local anesthesia. He made a good convalescence, without definite anginal attacks, and was discharged on the seventh day.

On April 28, 1927, he reported that he had felt distinctly improved by the operation, and had resumed work. He was able to walk several miles a day. He had had only one attack at night, but sometimes took one or two tablets a day and sometimes none at all.

The pain when it occurred was bearable. He now felt it first to the right of the sternum, along the fourth costal cartilage. His left eyelid drooped rather conspicuously, but he had no difficulty with his eyesight. He had had pain under the left jaw on beginning to eat, but this was sometimes severe. The skin was not hyperesthetic.

On May 11, 1928, the patient wrote that he felt perfectly well and had had no pain for many months. He had not taken any nitroglycerin tablets since August, 1927. He was working every day, and carried sample rolls when necessary. He was able to bowl with large balls and did anything he ever did, except to run for a train.

Comment. We should class him as 100 per cent relieved when last heard from. Why the late result should be better than the immediate effect of operation in this case is not at all clear. It is possible that some of the relief may have been a spontaneous recovery although the chief responsibility for his improvement must rest with the operation.

Discussion. Among 8 cases having 11 operations, there were 2 operative deaths, a mortality rate of 25 per cent of cases, and 19 per cent of operations. This death rate might have been reduced by a better selection of anesthesia. Cutler⁶ found the immediate mortality of sympathectomy in 120 collected cases of angina pectoris to be 5.8 per cent. In our series, lasting benefit followed operation in 4 cases, and was directly attributable to it in 3. In only 1 case out of 5 did satisfactory relief follow removal of the left superior cervical ganglion alone, although another (Case V) was considerably improved. In the other 2 patients benefited (Cases II and VI), afferent connections from the heart must have been severed to a greater or less extent (Table I).

TABLE I.—CASES TREATED BY SYMPATHECTOMY AT THE MASSACHUSETTS GENERAL HOSPITAL.

Operation.	Deaths.	Failures.	Lasting improvement.
Removal of superior ganglion, Cases I, V, VI, VII, VIII . . .	0	3	2 (Case V, 50 per cent) (Case VIII, 100 per cent)
Removal of cervical sympathetic chain, Cases II, III . . .	0	1	1 (Case II, 90 per cent)
Removal of inferior cervical and first thoracic ganglia, Cases I, VI . . .	1	0	1 (Case VI, 60 per cent)
Incomplete Operation, Case IV . .	1	—	—
	2	4	4

During the course of operation, no constant effect on the blood pressure or pulse rate was noted as a result of manipulation of the sympathetic chain. The excitement and mental strain of going through operation, even under local anesthesia, did not in any case precipitate an anginal attack. Horner's syndrome was regularly produced but there was no obvious change in the superficial circulation of the face. The blood pressure in the two arms was approximately equal, even in the case surviving removal of the stellate ganglion.

The fleeting cessation of attacks of pain following operation was interesting, and seemed more definite in patients receiving ether anesthesia than in those operated on under novocain. It shows that relief of pain immediately following operation should not be attributed in all cases to nerve section.

Pain in the region of the left jaw on beginning to eat was present in half the cases, but was troublesome rather than serious. Painful hyperesthesia occurred less frequently, and was distressing in only 1 patient (Case VI). Such after effects tended to disappear with time. These patients have apparently been little conscious of the change in the left eye. There was an occasional complaint of the lid drooping, or of the eye watering in the wind.

If the cases are grouped on a probable etiologic basis, there are 4 syphilitic cases, I, III, IV and VI. Of these, 2 died following operation, 1 was totally unrelieved, and 1, Case VI, was eventually partially relieved and enabled to work, but his improvement occurred so long after operation that some doubt must remain whether it was due to his operation or to further antiluetic treatment. This patient is the only one of the syphilitic group still alive, thirty-three months after his first operation.

Of 3 cases, II, VII, VIII, arteriosclerotic in origin, 2 were alive and greatly relieved, 1 after fifty-seven months, and the other after seventeen months. One case died seven weeks after operation, apparently of coronary thrombosis.

In 1 rheumatic case, Case V, the relief (50 per cent) obtained from

removal of the left superior ganglion was perhaps hardly enough to justify the operative discomfort and risk.

While these cases are too few in number to draw general conclusions, it would nevertheless suggest that syphilitic cases are poorer risks for operation, and also that the relief obtained may be less than in cases with an arteriosclerotic basis for their symptoms. Or, if we include Case V, it is possible that anginal pain, associated with dilatation of the aorta or with aortic regurgitation, may be less amenable to relief through sympathectomy than when occurring without this complication.

On considering these results early in 1927, we were on the whole not greatly encouraged in continuing with sympathectomy in angina pectoris. While relief had been occasionally obtained it had been at the expense of too great risk to the patient. We were particularly disappointed in the effect of removal of the superior cervical ganglion only, from which good results had been reported in the literature. The by-effects of operation, eye changes and hyperesthesia, did not greatly influence us, since the patients, unintellectual it is true for the most part, did not complain of their eye trouble, and the painful hyperesthesia tended to wear away. But it made a great difference whether removal of the superior ganglion alone, which could usually be done with care under local anesthesia, was effective, or whether it was necessary to remove the inferior cervical and first thoracic ganglia, a much more considerable procedure.

Our feeling was that the removal of the left superior ganglion only was in our hands too uncertain in its effect on pain to be recommended. More definite benefit should be obtained to justify the operative risk. When the sympathetic chain is exposed through an adequate incision, it is not difficult to remove it all, including the first thoracic ganglion. Opinions differ as to the effect of this procedure. Danielopolu¹⁶ believes that the operation intercepts the cardiac accelerator fibers and the cardiac and pulmonary vasomotor nerves, and that excision of the first thoracic ganglion seriously affects the physiology of the myocardium. The opinion of Leriche's Clinic, as expressed by Fontaine,⁵ is that after removal of the stellate ganglion, the heart will be adequate for its usual work, which it regulates, thanks to its intracardiac nervous apparatus, but it will be unable to accommodate itself to abnormal conditions, whether created by excessive work or by pathologic processes. These authors have suggested operations planned to sever only the sensory connections of the heart. But fears as to the competence of the heart have hardly been borne out by clinical experience. On the experimental side, Cutler⁷ states that dogs in whom the cervical sympathetic chain and stellate ganglia have been eradicated showed that their activity, well-being and response to exercise were equal to control animals. Cannon's¹⁷ experience with animals having complete sympathetic denervation does not suggest harmful effects from interruption of sympathetic control in man.

We were considering, therefore, the advisability of a more extensive removal of the sympathetic connection of the heart as a primary procedure. In this we feared not so much the ultimate physiologic effect of the operation as the immediate dangers of a somewhat extensive dissection requiring general anesthesia and displacement of the great vessels at the root of the neck in patients who are as a class bad risks. As an alternative means of treatment, it was decided to try the effects of paravertebral injection of alcohol as advocated by Swetlow.⁸ The results obtained have been reported by J. C. White and P. D. White,⁹ and by W. J. Mixter and J. C. White,¹⁰ and will be briefly summarized here for the sake of comparison.*

Altogether 8 cases have been treated by this means, 2 of them receiving two injections. The results obtained are summarized in Table II. These cases as a whole are comparable in seriousness to those treated by operation; the patients were either incapacitated or bedridden on account of the severity and frequency of their attacks. Three of them had coronary thrombosis and so would not have been suitable risks for operation; they survived the paravertebral alcohol injection without difficulty.

The point of attack in paravertebral injections of alcohol, the rami communicantes of the upper thoracic nerves, is anatomically sound with regard to interruption of the afferent impulses from the heart. The method has the obvious disadvantages of any blind destructive procedure, in particular the possibility of injury of the spinal cord by diffusion or misplaced injection. Special skill and experience is naturally required. We can only say that no lasting ill effects have as yet occurred. In 2 cases, rather alarming immediate effects were observed; in 1 a considerable fall in blood pressure, in another severe pain presumably from pleural irritation. Against these possibilities must be balanced the mortality of sympathectomy. With regard to relatively minor disadvantages, Horner's syndrome also follows paravertebral injection, particularly in successful cases. Regional hyperesthesia, although more constantly produced, appears less lasting than after sympathectomy. From this point of view, there is apparently little choice. The shorter hospital stay required following injection is a slight advantage. Injection so far as the experience of this clinic goes, has the definite advantage of being a safer procedure.

Symptomatic relief has more constantly been secured by paravertebral injections than by operation in our series of cases. While there has been a tendency for pain to recur in 1 or 2 cases, the relief has generally lasted as long as the patients have been followed, up to eighteen months in 1 case. Against this possibility of recurrence may be set the possibility of repeating the treatment when necessary.

* We are very grateful to Dr. J. C. White and Dr. W. J. Mixter for permission to include their material in this paper.

TABLE II.—CASES TREATED BY PARAVERTEBRAL ALCOHOL INJECTIONS AT THE MASSACHUSETTS GENERAL HOSPITAL.

Case.	Diagnosis.	Age, sex.	Treatments.	Result.	Degree relieved.	Duration.	Status at last report.
I (E. M.)	Syphilitic aortitis, aortic regurgitation, hypertension, angina pectoris; confined to bed	54 M.	Left 2/19/27; right 3/20/28	Left-sided relief; development of right-sided pain; no relief	100 per cent (left side)	To date	Up and about July, 1928, but unable to work; moderate attacks of right-sided pain.
II (H. T.)	Hypertensive and arteriosclerotic heart disease; aortic regurgitation, angina pectoris; previous attack of coronary occlusion; slight congestive failure	60 M.	Left 5/16/27; reinjection 6/23/27	Considerably relieved; further relief	0 per cent (right side) 50 per cent	To death	Able to resume light work; until sudden death, undoubtedly from coronary thrombosis or angina pectoris February 8, 1928; no autopsy.
III (M. K.)	Arteriosclerotic heart disease; hypertension; angina pectoris at rest	53 F.	Left 6/9/27	Relief slight but definite; difficult to judge because of extreme nervousness	20 per cent	To date	Up and about, quietly active, but with moderate angina pectoris, July, 1928.
IV (S. F. B.)	Moderate arteriosclerosis and enlarged heart; angina pectoris; incapacitated	54 M.	Left 7/22/27	Left-sided relief; mild right-sided attacks	100 per cent (left side)	To date	In fair health, June, 1928, but still has right-sided angina pectoris; has resumed work as truck driver.
V (E. C.)	Arteriosclerotic heart disease; hypertension; myocardial infarction; previous coronary thrombosis	59 M.	Left 8/12/27	Relief partial	25 per cent	To death	Died suddenly, January 9, 1928, undoubtedly of coronary thrombosis or angina pectoris; no autopsy.
VI (H. C.)	Hypertensive heart disease; aortic regurgitation; angina pectoris at rest	52 M.	Left 11/5/27	Complete relief at first (few months); later slight recurrence	100 per cent	To date	Comfortable and able to do light work, August 1, 1928.
VII (L. A.)	Arteriosclerotic heart disease; hypertension, angina pectoris	58 M.	Right 3/3/28	Considerable relief	90 per cent 65 per cent	To date	Fairly comfortable and has resumed light work, August, 1928.
VIII (C. Y.)	Arteriosclerotic heart disease; hypertension; angina pectoris; previous coronary thrombosis	68 M.	Left 4/17/28	Partial relief at first, then recurrence; judgment of case somewhat difficult because of much nervousness	75 per cent 50 per cent	To date	Uncomfortable, angina pectoris daily but able to be quietly up and about, July, 1928.

In 2 cases, classed as 100 per cent relieved, this benefit applied only to the side first injected. They continued to have right-sided attacks, milder in nature, and consequently were not so completely relieved as the 2 best cases following operation (Cases II and VIII).

In only 1 instance, did injection (Case VI) secure as good a general result as in the 2 operated Cases II and VIII.

Treatment of anginal pain by paravertebral alcohol injection we believe, therefore, at present to be superior to sympathectomy. No case has been treated by operation here since the injections were first tried. Whether or not a return to direct operative methods will be made as a supplementary procedure under special indications cannot as yet be said. At least we have not tried the combination.

The broad question remains as to whether any good has been accomplished by these destructive measures. We feel on the whole that there has been benefit, in spite of the two operative fatalities. Suffering has been relieved, bedridden patients have been restored to activity, and a few individuals, operated Cases II, VI and VIII and injected Cases IV, VI and VII, have been returned to economic usefulness. Nor can it be said definitely that this has been at the expense of further damage to the circulatory apparatus, or of harmful overexertion, due to absence of the warning pain. While deaths have occurred some months after operation, it is not clear that those patients who survived treatment have been more subject to accidents congestive failure, coronary thrombosis, or sudden fatality, than might be expected in a group of equally severe anginal cases treated conservatively.* We believe that treatment by paravertebral injection is justifiable in carefully selected patients who do not respond to other forms of treatment.

The selection of cases, therefore, is the most important aspect of the situation. It may be summarized as follows: Paravertebral alcohol injection, generally of the left upper five thoracic nerve roots, may be recommended in the treatment of obstinate angina pectoris which persists in spite of ample medical measures, and which renders work impossible and life miserable. Given these indications there seem to be no contraindications. The injections may be made even after coronary thrombosis, and doubtless are much less of a risk than is cervical sympathectomy. It is quite possible that failure of a paravertebral alcohol injection may justify operative procedures but our experience to date would indicate that the therapy of first choice for angina pectoris when medical measures have failed is the injection method.

* We have seen one case, however, operated elsewhere (left cervical sympathectomy) with almost complete (95 per cent) abolition of the angina pectoris, who undoubtedly was too active as the result of his freedom from pain and who died from congestive failure six months after the operation. How much longer he would have lived had he remained very quiet or whether his angina pectoris would have killed him sooner had he not been operated are questions which must remain unanswered.

Conclusions. (1) The pain of angina pectoris may be modified or abolished by operation on the cervicothoracic sympathetic system, or by paravertebral injection of alcohol.

2. That the relief of pain or interruption of the nervous mechanism of the heart exerts a harmful effect on the course of the disease, although possible, is not proved.

3. Paravertebral injection of alcohol appears safer than operation upon the sympathetic connections of the heart in the treatment of angina pectoris.

4. In carefully selected cases, refractory to other measures, further observations on the effect of paravertebral injections of alcohol are justified.

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THE SYMPTOM OF SIGHING IN CARDIOVASCULAR DIAGNOSIS.*† WITH SPIROGRAPHIC OBSERVATIONS.

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For the diagnosis of effort syndrome, neurocirculatory asthenia, cardiac neurosis, nervousness and fatigue the symptom of sighing is a useful but much neglected aid, especially in differentiating these conditions from disability due to cardiovascular disease. Its very frequency and simplicity have doubtless led to its neglect. About five years ago our attention was attracted to the value of observation and inquiry of the frequency and degree of sighing and for the last two years the symptom has been routinely looked and asked for in the examination of patients. On several occasions, indeed, we have even been asked to see in consultation patients whose only symptom or sign was constant sighing. Because of the scarcity of data on sighing and of the lack of knowledge of its application to internal medicine, we have made a study of it from certain points of view during the past year, especially as to its place in cardiovascular diagnosis. It is this study that we are reporting here.

A sigh (Latin, *suspirium*) is best defined as follows (Webster's Dictionary, 1924) "A single, deep, prolonged, audible respiration, especially as the involuntary expression of fatigue, exhaustion, grief, sorrow, or pleasure."

We have searched many of the best known authoritative medical works, past and present, especially those dealing with the heart, and but rarely have we found any reference, even in passing, to this interesting symptom. Graham Steell¹ and Crummer² have written of it briefly as follows. Steell,¹ in 1906, said "A peculiar and also rare variety of dyspnea—if such it can be called—is that which causes the patient in repose to take occasionally a very deep breath or 'sigh.' This occurrence was described many years ago, and was then associated with fatty degeneration of the heart muscle. The patient is hardly aware of any feeling of dyspnea, and the long drawn breath is largely automatic, but there is probably generally some slight subjective sensation of 'air hunger'." Crummer,² in

* Presented in abstract at the annual meeting of the American Society for Clinical Investigation, Washington, D. C., April 30, 1928.

† Fourth of a series of papers from the Massachusetts General Hospital on Clinical Spirography.

1925, said "Dyspnea of purely nervous origin may be experienced as a thoroughly disagreeable sensation by such patients. Two simple types of nervous dyspnea may be recognized. In the first, a sighing respiration occasionally interrupts the sequence of breathing and is preceded in the patient's consciousness by a sensation amounting to air hunger. In the second, there are periods of increased rapidity with shallow breathing, which is aptly described by the word panting."

It has been our experience, both before and during the special study to be recounted here, that whereas dyspnea, palpitation, and heart pain may be due either to heart disease or to fatigue or nervousness, sighing is never due primarily to heart disease but always to fatigue or nervousness or other such factor. Thus it is at times of great value as a symptom in the differential diagnosis of cardiovascular disease, and along with dizziness, faintness and tremor helps to diagnose effort syndrome. Even when heart disease has been found to be present the symptom of sighing aids much in the determination of the percentage of responsibility of heart and nervous system in the production of disability in a given case.

As we already have said, sighing is frequent. Nearly everyone sighs at times under certain provocation. Also it may be a habit in a few people, even in earliest childhood. The degree and frequency of sighing in a given individual, and not its mere existence, are what determine its importance as a symptom, just as thirst and drowsiness, if excessive, may become important symptoms of disease.

Present Study. The first part of our study of sighing has included observation and inquiry of its frequency in 650 people, mostly adults, of whom 400 were normal controls, nearly all young men and women, 100 were cases of organic heart disease who were not especially nervous or tired (half of whom had congestive failure and half had not), 100 were cases of nervous fatigue or effort syndrome without heart disease, and 50 were cases with both organic heart disease and effort syndrome.

The second part of our study has concerned itself with graphic records of the respiration (spiograms) taken to determine the frequency of sighing, or reviewed when taken in the past to determine the condition of the cases who showed increased sighing. The spiograms were obtained as in the routine method of determining the basal metabolic rate.

We have used as a criterion of frequent sighing a lower limit of at least ten respirations on the spiogram which were 50 per cent or more deeper than the usual respirations in the course of ten minutes, or at least five respirations twice as great or more than the usual in this same interval of time. Many normal people show one or two increased respirations in the course of ten minutes, but many more show no increase at all. There are borderline cases but we

have set the limit sufficiently above the usual normal to be very significant.

Thirteen of the cases of organic heart disease without nervous fatigue were traced in this way, 8 of those with congestive failure and 5 without; 8 of the cases of effort syndrome were so traced; graphic records were also made from 12 of the control cases without either heart disease or effort syndrome, and from 8 of the group of combined heart disease and effort syndrome. Thus 41 cases from all four groups were traced. Two hundred spiograms already taken in the past were reviewed to determine the diagnoses in cases showing well-marked sighing. Ten cases of hyperthyroidism and 10 of hypothyroidism were studied also by graphic record. Finally, the state of the blood gases was studied in 2 of the cases showing much sighing.

Results of Study. I. *Statistics.* Four hundred healthy adults without heart disease were asked about the frequency with which they sighed. Fifty did not know whether they sighed or not, 42 said that they did not sigh, 77 that they sighed rarely and 155 that they sighed occasionally. Seventy-six, or 19 per cent, stated that they sighed frequently.

Sixty of these 400 control cases were school boys, fifteen to nineteen years; 9 of them (15 per cent) sighed frequently. One hundred and six were young men studying medicine, twenty-one to twenty-nine years of age; 11 of them (10 per cent) sighed frequently. One hundred and eighteen were school girls fifteen to twenty years of age; 20 of them (17 per cent) sighed frequently. One hundred and eight were young women in college, eighteen to thirty-two years of age; 36 of them (33 per cent) sighed frequently. Evidently under ordinary conditions, therefore, young women in the third decade of life are likely to sigh often. Mitral stenosis in such individuals should not be wrongly blamed for this natural tendency to nervous and cardiovascular symptoms. The causes cited, in the order of their frequency, which were thought responsible by these control cases for their sighing were mental fatigue, physical or mental fatigue or both, "unknown" depression, relief, disgust, disagreeable tasks, physical fatigue, worry, emotional distress, exasperation, overeating, disappointment, boredom, insufficient sleep, unhappiness, examinations, and long lectures.

Of 100 patients with organic heart disease with and without congestive failure who were not nervous, 24 were found to sigh, but the symptom was a frequent one in only 3 (3 per cent), 2 of whom were young females without congestive failure and the other one a middle-aged man with congestive failure.

Of 100 patients with effort syndrome, nervous fatigue, or excessive nervousness, without heart disease, all but 9 stated that they sighed and the sighing was frequent in 80 (80 per cent), of whom

51 were women, 33 under the age of forty years. Four of the effort syndrome cases, one girl aged fourteen years, one boy aged fourteen years, and two men, one young and one middle-aged sighed excessively, the symptom of sighing being the chief complaint.

Finally of 50 cases of heart disease and effort syndrome combined only 3 denied sighing, while in 37 (74 per cent) it was a frequent occurrence. Thirty-seven of the 50 cases were women and 29 of them sighed often (78 per cent); 13 were men and 8 of them sighed frequently (62 per cent). All ages were represented. In 2 cases

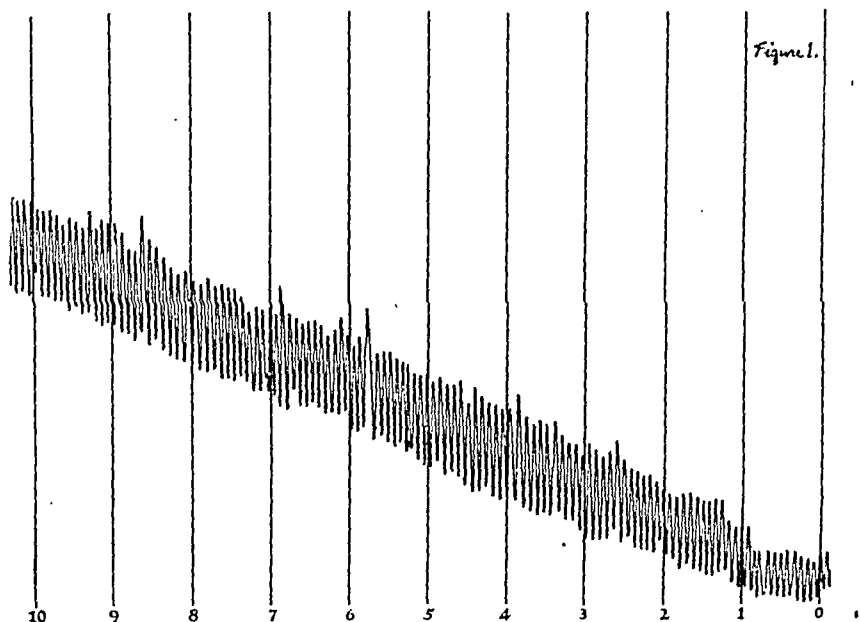


FIG. 1.—Respiratory tracing from a young woman with organic heart disease (mitral stenosis) without congestive failure or nervousness. As in the remaining figures, the tracing reads from right to left and the time intervals mark off minutes. No deep respirations or sighs are present in this tracing although a few breaths are a little fuller than the others. The respiratory rate is 12 per minute. The tracing covers a ten-minute period.

(females one young and one middle-aged) sighing was the chief complaint. In almost all of these 50 cases the nervous factor was much more responsible than the cardiac factor for any disability present.

II. Respiratory Tracings. Respiratory tracings were taken for intervals of ten minutes from 41 cases representing all four groups: (1) Control cases without either heart disease or effort syndrome; (2) cases of organic heart disease without nervousness or effort syndrome; (3) cases of effort syndrome without heart disease, and (4) cases of heart disease and marked nervousness or effort syndrome. These tracings fully confirmed the statistical data.

Of the 5 cases with organic heart disease without effort syndrome or congestive failure who were traced, none showed abnormal sighing (0 per cent). A typical example is given in Fig. 1.

Of the 8 cases with organic heart disease without effort syndrome but with congestive failure, none showed abnormal sighing (0 per cent). Typical examples are given in Figs. 2 and 3. This finding is especially significant because all these patients were suffering from dyspnea, distressing in several and Cheyne-Stokes in character in one.

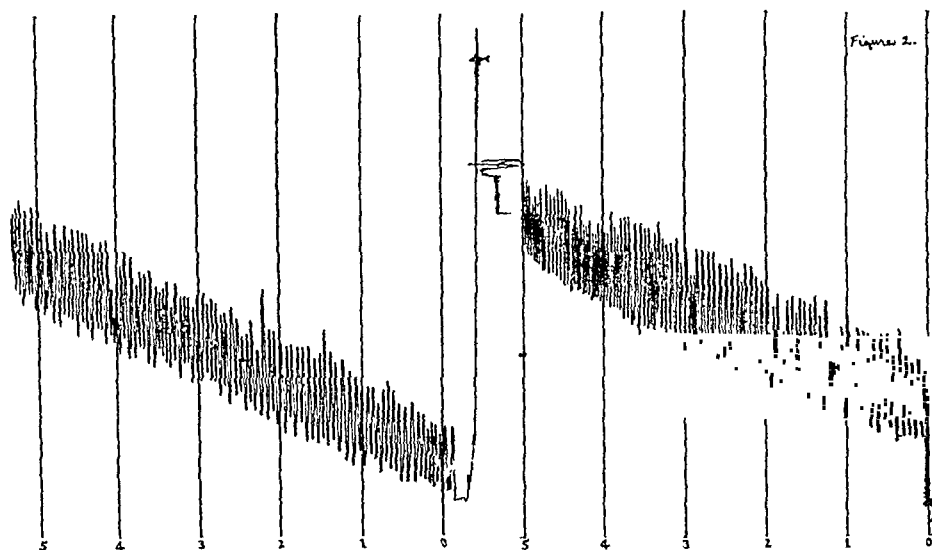


FIG. 2.—Respiratory tracing from a middle-aged woman with organic heart disease (hypertensive, arteriosclerotic type) with congestive failure. After the first period of five minutes dyspnea became so marked that the tracing was stopped for a rest period, and this was followed shortly by a second five-minute tracing. The respiratory rate increased in each of the strips of tracing, from 13 to 26 per minute in the first and from 15 to 19 in the second. In spite of the dyspnea no sighing respirations occurred.

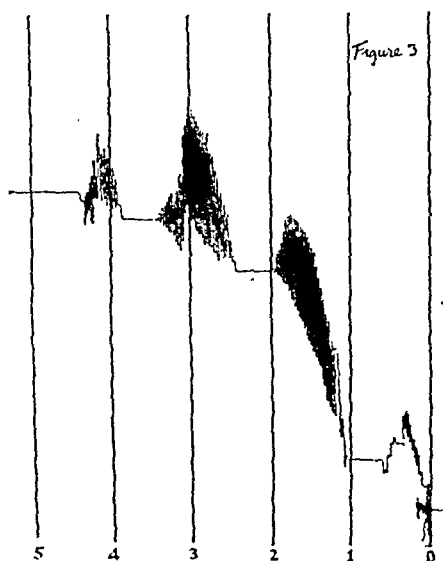


FIG. 3.—Respiratory tracing from an elderly man with organic heart disease (hypertensive-arteriosclerotic type, with auricular fibrillation) showing congestive failure and Cheyne-Stokes respiration. A period of five minutes is represented with four cycles of hyperpnea and apnea. No sighs occurred.

Of the 8 cases with effort syndrome or marked nervousness without organic heart disease, 6 showed abnormal sighing (75 per cent). Typical examples are given in Figs. 4 and 5.

Of the 8 cases with both effort syndrome or marked nervousness and heart disease 6 showed abnormal sighing (75 per cent). A typical example is given in Fig. 6.

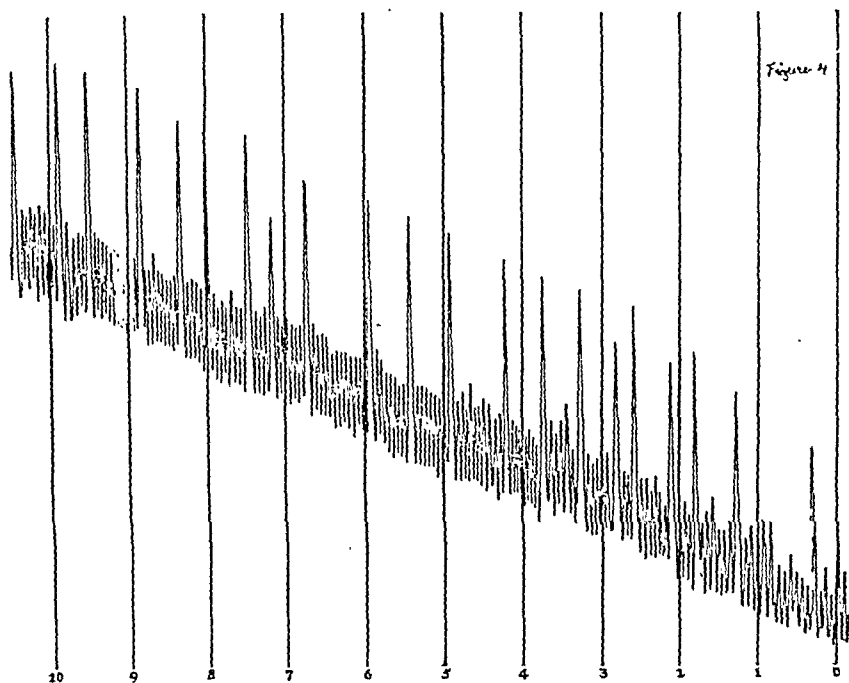


FIG. 4.—Respiratory tracing from patient (a middle-aged woman) with effort syndrome and marked nervousness without heart disease. In the period of ten minutes twenty deep prolonged respirations (sighs) occurred. The respiratory rate varied from 13 to 16 per minute. Total ventilation was somewhat increased above the average.

Of the 12 control cases without either heart disease or effort syndrome or marked nervousness who were traced none showed abnormal sighing (0 per cent). Typical examples are given in Figs. 7 and 8.

After these groups had been studied and their spiograms obtained, 200 routine unselected respiratory tracings on file in the Metabolism Laboratory at the Massachusetts General Hospital were examined, with the kind permission of Drs. Means and Thompson and the assistance of Miss Hardy.

Of these 200 tracings, 35 were found to show an abnormal degree of respiratory irregularity in accord with the criteria of abnormal sighing already noted. The diagnoses in these 35 cases were found to be psychoneurosis in 5, hyperthyroidism in 5, pituitary disease in 3, nontoxic thyroid adenoma in 2, and scattered in the remainder. The scattered diagnoses included neurasthenia, visceroptosis,

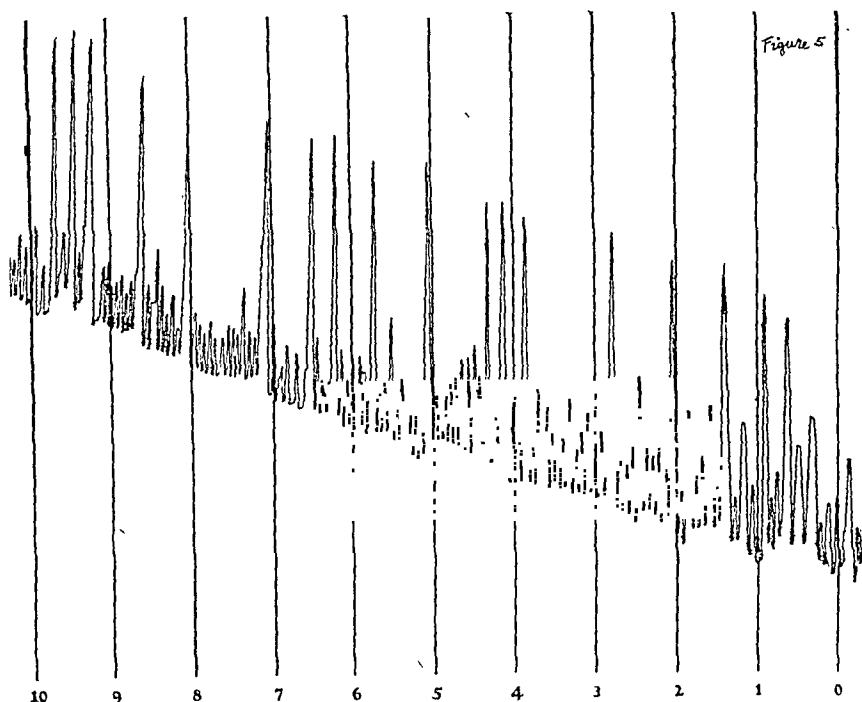


FIG. 5.—Respiratory tracing from a girl, aged sixteen years with marked effort syndrome and no heart disease. She had been seen in consultation because of the chief complaint of constant and marked sighing. No disease was found after careful study in the hospital. In the period of ten minutes 24 sighing respirations occurred. The respiratory rate was somewhat irregular, varying from 8 to 13. Many of the breaths were very small, compensating for the deep respirations, so that the total ventilation was within normal limits, averaging 8.6 liters per minute.

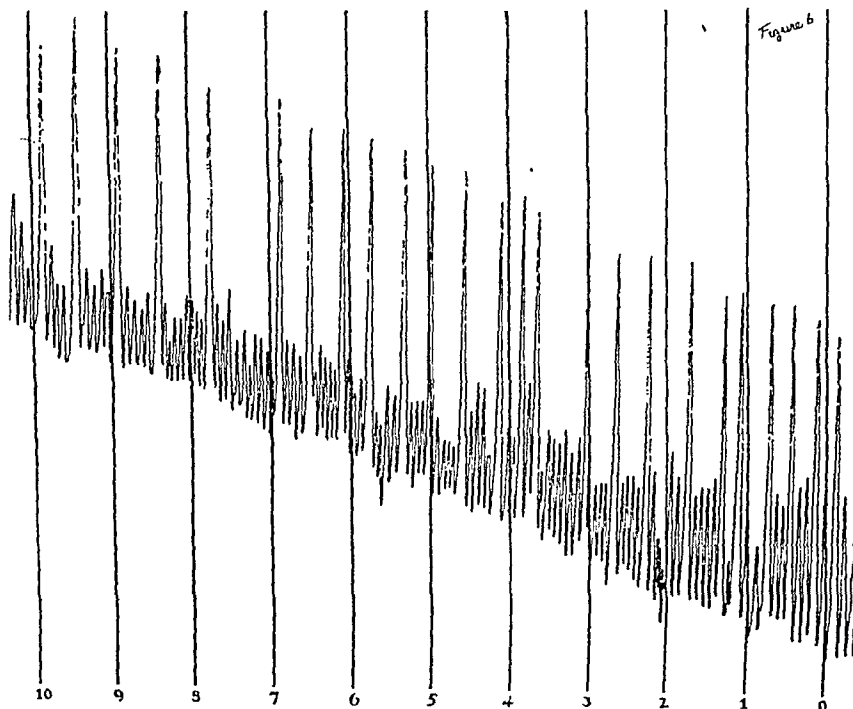


FIG. 6.—Respiratory tracing from a young woman with both heart disease (rheumatic aortic regurgitation) and marked nervousness. Note the large number of deep respirations (sighs), a total of 24 in ten minutes. The respiratory rate varied from 9 to 13 per minute.

poor posture, endocrine disorders, obesity, chronic arthritis, and so on. It is obvious that in this group of 35 positive records nervous instability, either primary or secondary, is the predominating factor. Heart disease was noteworthy by its absence.

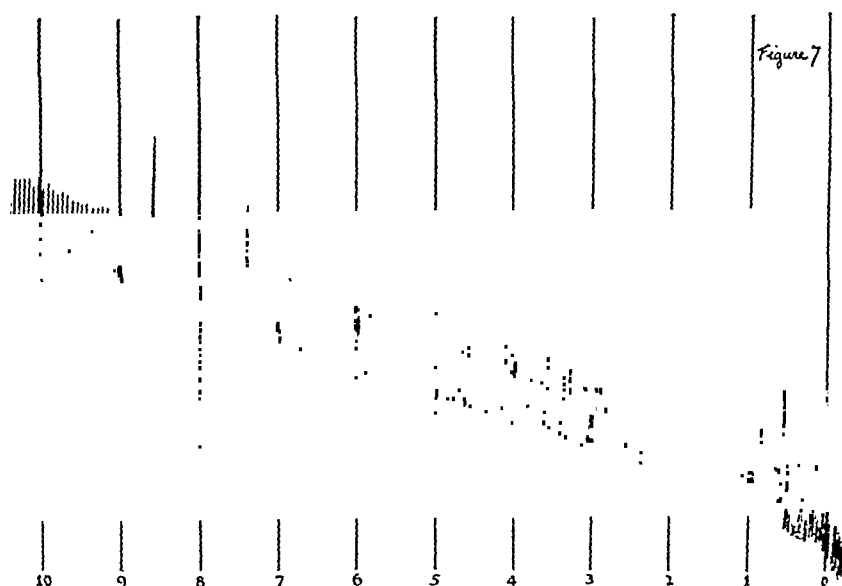


FIG. 7.—Respiratory tracing from patient (middle-aged woman) with a normal heart and without effort syndrome or nervousness. Three deeper breaths occurred in the interval of ten minutes. The respiratory rate was 16 (15 to 17).

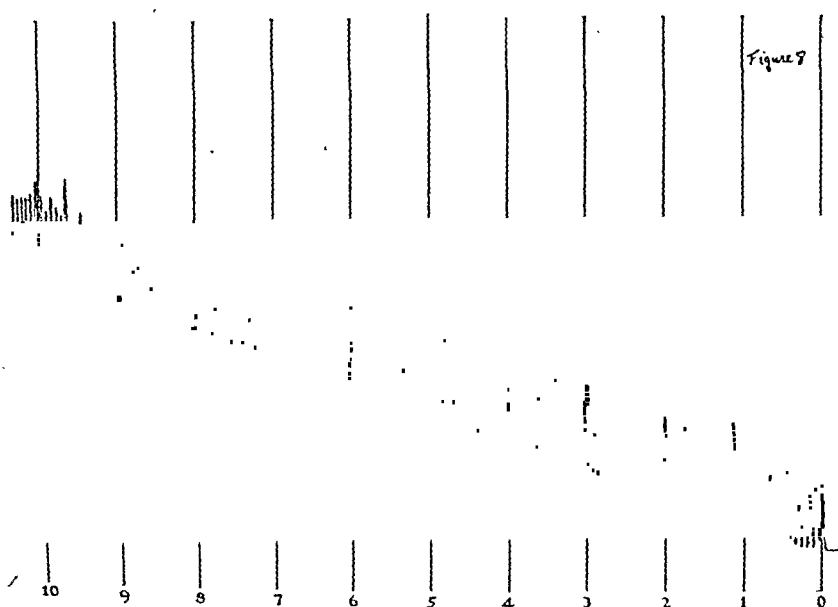


FIG. 8.—Respiratory tracing from a normal young woman (without effort syndrome or heart disease.) No sighs are noted although two breaths are slightly greater than the usual in the interval of ten minutes. The respiratory rate was 14 to 17 per minute.

To determine the frequency of excessive sighing in thyroid disease the spirograms of 10 cases of exophthalmic goiter and of 10 cases of myxedema were examined. Four of the hyperthyroid cases were positive (40 per cent) and 2 of the hypothyroid cases (20 per cent).

Finally, we studied the patients who sighed frequently to determine whether or not we could find any evidence of faulty action of kidneys, heart, lungs, or metabolism. None was apparent and we concluded that this symptom of sighing is solely a nervous phenomenon associated with fatigue or habit. In 2 cases with excessive sighing investigated there was no evidence of abnormal oxygen or carbon dioxide content in the blood.

Summary and Conclusions. 1. A study is here reported of the symptom of sighing, especially as it concerns cardiovascular diagnosis.

2. Statistical analysis showed that in four hundred normal control individuals sighing is a common finding, but of frequent occurrence in only 19 per cent. It was especially common as a frequent event in young women in the third decade of life (33 per cent), and it is generally recognized that it is this sex at this age that shows the greatest degree of nervous instability.

3. Further statistical analysis showed that frequent sighing is relatively rare in heart disease with or without congestive failure if there is no effort syndrome or marked nervousness (3 per cent of 100 cases).

4. In effort syndrome without heart disease excessive sighing is very frequent (80 per cent of 100 cases).

5. When effort syndrome or marked nervousness is combined with organic heart disease, excessive sighing is common (74 per cent of 50 cases). It is evident from the data previously cited that in these cases the sighing comes from the nervous state and not from heart disease.

6. Respiratory tracings from 5 cases of heart disease without congestive failure or nervousness showed an abnormal number of deep breaths in none; tracings from 8 cases of heart disease with congestive failure but without nervousness also showed an abnormal number of deep breaths in none; those from 8 cases of effort syndrome without heart disease showed an excessive number of deep breaths in 6 (75 per cent), those from 8 cases of combined effort syndrome or marked nervousness and heart disease showed increase of sighing respirations in 6 (75 per cent), and those from 12 cases without either effort syndrome or heart disease showed an abnormal number of deep breaths in none.

7. Of 200 routine unselected cases studied by respiratory tracings in the metabolism laboratory 25 showed abnormal sighing. Nervous instability was the commonest condition found in this group; no heart disease was present in any of the cases. Sighing was excessive

in 4 of 10 cases of hyperthyroidism and in 2 of 10 cases of hypothyroidism.

8. Frequent or constant sighing is a symptom of nervous origin, not dependent on disease of heart, lungs, kidneys, or thyroid gland. When it is present one should determine the degree of responsibility of the nervous system in the production of a state of ill health that may exist.

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BLOOD CHEMICAL STUDIES IN ARTERIAL HYPERTENSION.*

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THE theory that arterial hypertension is due to the presence of some powerful constrictor substance in the blood was clearly formulated by Sir George Johnson in 1868. Johnson expressed the belief that the cause of arterial hypertension was the continued contraction of arterioles and observed that "the minute arteries in any part of the body may be excited to contract by their contents becoming abnormal and therefore more or less noxious to the tissues." Johnson saw in the observations of Gowers a confirmation of his theory that contraction of the arterioles is the cause of increased arterial tension. In 5 successive cases of Bright's disease in different stages and with different degrees of tension, Gowers observed a direct relation between the contraction of the arterioles in the retina and the degree of arterial tension at the wrist. Gowers' observations were published in 1876.

Broadbent, in 1890, expressed his belief in the correctness of Johnson's views, stating that he considered hypertension to be due to an increased resistance in the capillaries, the cause of which "can scarcely be other than some substance present in the blood which acts directly upon the capillary walls." He adds that "the special material which plays this part is almost certainly nitrogenized waste which has not undergone the complete oxidation necessary for elimination."

* Read before the Annual Meeting of the Association of American Physicians in Washington, D. C., May 1, 1928.

Von Monakow, fifty years after Johnson's publications, and thirty years after Broadbent's, expressed his belief that a "lasting increase in blood pressure is always due to abnormal contractions of arterioles" and that there is a "spastic component" present. Otfried Müller shares the views of von Monakow and describes constriction of the capillaries in both nephritis and "essential hypertension." More recently, Brown and Roth have studied the capillaries in arterial hypertension and while they find in the majority of cases no characteristic morphologic changes, yet the rate of flow is faster than normal and they note a rapid alternation of fast and slow suggesting intermittent closure of vessels. They state the impression "that there is definite capillary and arteriolar hyper-tonus with disturbances in the tonus control of the precapillary vessels."

The theories of Johnson and of Broadbent, together with the observations of Gowers, von Monakow, Müller, Brown and Roth, and others have been a constant stimulus to investigators to study the chemistry of the blood in hypertension. This had led to an intensive study of the well-known chemical constituents of the blood in hypertensives and has stimulated search for some unknown pressor substance in the blood.

The observations of Neubauer that certain patients with high blood pressure had a hyperglycemia, attracted much attention and led to an intensive study of the blood sugar in arterial hypertension. Hitzenberger and Richter-Quittner found the blood sugar regularly elevated in "vascular hypertension," with the highest blood sugar in the patients with the most marked hypertension. Kahler, however, after an investigation of this subject, states that in the vast majority of cases of long-standing hypertension, the fasting blood sugar is within normal limits. He found hyperglycemia especially in the complications of hypertension, in apoplexy, eclampsia and uremia. He states also that "Hochdruckstauung" is regularly accompanied by a hyperglycemia.

We have investigated this subject of hyperglycemia in 161 cases of arterial hypertension, 7 of whom were diabetics. In 154 cases, only 9 (5.8 per cent) showed fasting blood sugar above 110 mg. per 100 cc. and only 6 (3.7 per cent) showed fasting blood sugar above 120 mg. per 100 cc., the figures being 130, 135, 136, 139, 141 and 152 mg. per 100 cc. If we accept 120 mg. per 100 cc. as the upper limit of the normal fasting blood sugar, we find only 3.7 per cent showing a hyperglycemia, which is a rather unimpressive total.

While it is an unquestioned fact that hypertension unaccompanied by chronic nephritis frequently shows a hyperglycemia, our observations in hypertension unaccompanied by evidences of renal insufficiency, in agreement with those of Kahler, indicate that the great majority of hypertensives show a normal blood sugar.

Joslin has advanced the interesting idea that the hyperglycemia

found in hypertension is the response of the body to the heart's increased demand for sugar in order to maintain its excessive work. The presence of a large, overactive heart or a certain degree of cardiac failure in hypertensives showing a hyperglycemia makes the explanation more reasonable perhaps than the assumption of an increased adrenal activity.

Fishberg found that many patients with essential hypertension showed an increased uric acid in the blood. This observation has been repeatedly confirmed and was noted by Hitzenger and Richter-Quittner and by Kraus. Fishberg studied 110 cases and found values higher than 3.5 mg. per 100 cc. in 44, or 39 per cent.

We have studied the blood uric acid in 170 cases of arterial hypertension, uncomplicated by frank nephritis. Of this number, 57 cases showed a blood uric acid above 5 mg. per 100 cc. and 113 cases above 4 mg. per 100 cc. If we accept 4 mg. per 100 cc. as the upper limit for normal, then 66 per cent of our series showed an increased blood uric acid. The highest value found was 10.5 mg., while 24 were 6 mg. or higher and 4 were 7 mg. or higher.

These observations indicate that while an increase in the blood uric acid is most striking in chronic nephritis, more than one-half of the cases of arterial hypertension who have no evidence of renal inadequacy show blood uric acid above the normal values.

Westphal has suggested that cholesterol may play a rôle in the production of high blood pressure and found a hypercholesterinemia in 71 per cent of 80 patients studied. Westphal believes that cholesterol increases the sensitiveness of the arterial musculature to adrenalin and in that way plays a rôle in hypertension. Hülse has been unable to confirm this work and thinks that while there may be a relationship between hypercholesterinemia and atherosclerosis, there is none between hypercholesterinemia and hypertension. Hülse noted that many patients with a hypercholesterinemia showed a marked atherosclerosis but no elevation in blood pressure.

Thomas has described an elevation in blood pressure produced by repeated injections of cholesterol into 4 rabbits. Thölldte, however, who repeated this work, obtained negative results and believes such results to represent only normal variations in pressure. Thölldte's conclusions seem quite warranted since the highest pressure recorded by Thomas was only 125 mm.

Kylin has been interested in the possible rôle of potassium and calcium in blood pressure. In hypertension, he has found a tendency for the blood potassium to be increased and the blood calcium to be lowered. This relationship of potassium to calcium, he has described as the K-Ca quotient. The quotient in health he finds to average 1.98, while in essential hypertension the average quotient is 2.33, and in bronchial asthma 2.48. The results obtained in bronchial asthma, together with other evidence, has led Kylin to the view that the autonomic nervous system plays an important rôle in the causation of essential hypertension.

The above observations showing that certain cases of arterial hypertension show increased amounts of blood sugar, blood uric acid and blood cholesterol, are of considerable interest, since they suggest possible metabolic disturbances in this disease. The difficulty in assigning a specific effect to them lies in the fact that neither glucose, uric acid nor cholesterol are pressor substances. It should be further recalled that diabetes, a disease in which the blood sugar is regularly increased, shows no elevation of blood pressure as a constant rule; that gout and leukemia, in which the blood uric acid is elevated, usually show normal blood-pressure values and that diseases in which the blood cholesterol is usually increased, such as cholelithiasis, lipoid nephrosis, atherosclerosis and diabetic acidosis do not show an increase in blood pressure as a constant or essential feature.

We have been studying for the past four years the possible rôle of the guanidin bases in the production of hypertension. It is well known that most of these bases, such as guanidin, methylguanidin and di-methylguanidin produce a marked rise of blood pressure when introduced into the body. It should be remembered, however, that certain guanidin derivatives, such as creatin and creatinin, have no specific effect upon blood pressure, while others, such as glycoyamin and glycoyamidin have a depressor effect. If the pressor guanidin compounds are present in the body in excessive amounts as the result of an increased production or a decreased excretion, they could produce a hypertension.

We have recently described a method by which small amounts of guanidin can be demonstrated in the blood. This method, which has been described elsewhere, is based upon the observations of Tiegs and Marston, that sodium nitroprusside produces in an alkaline solution an intense red color with guanidin compounds. We have applied this method to the study of the blood of persons with normal blood pressure, to that of patients suffering from chronic nephritis and to that of patients with so-called essential hypertension.

A study of 50 persons with normal blood pressure has shown us that the normal value for blood guanidin, if guanidin is present in the blood, does not exceed 0.2 mg. per 100 cc. and, as a rule, averages about 0.1 mg. per 100 cc.

The results obtained in 15 cases of chronic nephritis with hypertension are shown in Table I.

A summary of this table shows that all the cases of chronic nephritis with hypertension show a marked increase in "blood guanidin." This increase may, of course, be due to an oxidation in the body of creatinin into methylguanidin, although we have good evidence that it is not due to oxidation produced by the method employed. It is also important to remark that if the high blood values obtained in certain nephritics are actually due to guanidin, then guanidin is present in sufficient amounts to produce toxic symptoms such as convulsions.

TABLE I.—GUANIDIN READINGS IN A SERIES OF 15 PATIENTS WITH NEPHRITIS.*

No.	Age.	Blood pressure.	N.P.N.	Creatinin.	Creatinin.	Uric acid.	Guanidin readings.	Guanidin corrected.	Remarks.
1	51	194/130	86.0	3.6	5.1	..	0.05	0.39	Uremia.
2	62	220/110	168.0	9.7	9.0	16.0	1.01	0.93	
3	51	165/90	167.0	3.0	7.5	13.4	0.95	0.89	
4	51	180/120	67.0	3.8	..	7.0	0.37	0.27	
5	58	158/110	52.0	2.1	..	7.2	0.55	0.39	
6	60	180/90	39.0	1.4	0.46	0.43	Carcinoma of cervix.
7	40	260/150	131.0	11.7	..	8.8	0.46	0.41	
8	48	170/110	60.0	2.5	2.6	..	0.52	0.29	
9	64	240/145	74.0	2.7	6.0	4.7	0.49	0.37	
10	14	142/115	40.0	1.5	3.6	5.7	0.36	0.32	
11	42	140/88	83.0	6.5	0.75	0.69	Urea N. 75.
12	38	220/120	96.4	4.6	0.49	0.28	
13	40	180/130	315.0	12.0	5.6	5.3	1.1	0.67	
..	..	170/120	183.0	18.5	..	8.0	2.4	2.3	Uremia.
14	27	200/140	97.8	8.3	..	4.7	0.49	0.28	
..	..	200/140	89.0	11.0	1.4	3.9	0.67	0.54	
..	..	180/130	77.0	8.7	6.7	5.0	0.94	0.45	Uremia.
15	24	160/110	188.0	13.7	2.3	..	1.6	1.3	

* Blood chemistry in milligrams per 100 cc. of blood.

In Table II are shown the results obtained in 80 cases of hypertension belonging to the group of hypertension usually described as essential hypertension, in which there is no evidence of severe renal impairment and in which the blood nonprotein nitrogen and creatinin are within normal limits.

A summary of this table shows that 61 per cent of the patients have a "blood guanidin" higher than normal. These increases, while not very striking, are significant if the increased color is due to guanidin, since animals, when injected with methylguanidin, show a marked rise in blood pressure when the concentration of guanidin in the blood reaches the height which many of these patients show. Observations upon this phase of the subject have been reported elsewhere.

We wish to emphasize that we have no proof that this color reaction is produced by guanidin compounds. Such proof would only come with the isolation of guanidin from the blood, a very difficult procedure when the amounts are so minute.

It is also possible that this color reaction may be a delicate index of the renal function and that the increased amounts are due to a renal insufficiency not detectable by the usual tests of kidney function. But here again, if we are dealing with guanidin, these results should throw some light upon the etiology of arterial hypertension.

The 39 per cent of patients with hypertension, showing normal blood-guanidin values, is also an interesting group about which to speculate. Many of them were old people showing marked arteriosclerosis, who may have developed their hypertension during a

TABLE II.—GUANIDIN READINGS IN A SERIES OF 80 PATIENTS WITH ARTERIAL HYPERTENSION.*

No.	Age.	Blood pressure.	N.P.N.	Creatinin.	Creatin.	Uric acid.	Guanidin readings.	Guanidin corrected.	Remarks.
1	54	180/120	40.0	1.6	5.6	5.0	0.57	0.14	
2	50	156/110	35.7	1.3	4.9	3.1	0.44	0.27	
3	36	200/134	33.3	1.4	5.2	4.0	0.44	0.28	
4	74	176/110	30.0	1.3	4.6	3.3	0.22	0.13	Marked arteriosclerosis.
5	70	192/130	37.0	1.3	3.1	4.1	0.33	0.16	Marked arteriosclerosis.
6	40	176/110	37.5	2.0	4.5	5.4	0.36	0.09	Diabetes.
7	48	190/112	35.0	1.5	4.8	4.1	0.42	0.13	Carcinoma of breast.
8	72	175/110	29.0	1.4	3.8	2.4	0.23	0.04	Arteriosclerosis.
9	51	194/130	86.0	3.6	5.1	5.3	0.65	0.39	
10	45	210/100	33.0	1.2	3.0	2.7	0.38	0.2	
11	47	180/120	30.0	1.1	2.9	..	0.38	0.21	
12	63	196/98	31.0	1.3	2.7	3.2	0.33	0.12	Aortic insufficiency.
13	34	180/110	28.7	1.3	5.0	3.3	0.4	0.1	
14	44	185/120	28.0	1.2	3.8	3.6	0.48	0.25	
15	48	144/80	48.0	1.7	4.5	5.1	0.6	0.33	
16	57	190/130	39.6	1.4	4.5	3.46	0.34	0.07	
17	30	160/120	37.0	3.0	3.3	2.75	0.38	0.18	
18	57	178/124	37.5	2.4	3.0	3.2	0.43	0.25	
19	65	180/120	33.0	1.3	4.2	6.1	0.32	0.26	
20	55	178/95	35.0	1.3	3.7	4.7	0.32	0.25	
21	66	214/130	36.5	1.1	3.2	..	0.44	0.28	
22	66	214/130	36.5	1.1	3.2	..	0.44	0.28	
..	..	220/134	33.0	1.3	0.42	0.3	
23	35	240/140	91.0	4.9	5.1	6.1	0.46	0.15	
..	156.0	9.6	10.0	9.4	1.2	0.68	
24	42	190/120	92.0	4.3	3.5	..	0.46	0.25	
..	..	170/110	31.0	1.2	6.2	..	0.56	0.3	
25	47	180/120	40.0	1.9	0.62	0.48	
26	68	234/130	33.0	1.2	5.6	4.1	0.55	0.29	
27	32	255/145	30.0	1.5	4.3	3.6	0.31	0.14	
28	54	180/120	34.0	1.2	4.6	6.0	0.31	0.19	
29	43	180/120	30.0	1.6	5.3	3.8	0.27	0.16	
30	42	170/110	31.0	1.5	5.1	4.9	0.36	0.17	
31	39	240/130	35.3	1.8	4.0	4.9	0.33	0.22	
32	65	200/130	71.0	2.6	3.5	..	6.33	0.2	
33	37	200/134	33.0	1.4	5.2	4.0	0.44	0.32	
34	70	192/130	37.0	1.3	4.4	4.1	0.33	0.17	
35	56	216/92	40.0	1.8	..	5.2	0.37	0.12	
36	72	200/120	48.0	1.3	5.0	3.2	0.41	0.19	
37	50	178/130	33.0	1.2	4.7	4.2	0.33	0.20	
38	43	180/110	30.0	1.6	5.3	3.8	0.27	0.16	
39	40	180/100	31.0	1.5	5.1	4.9	0.36	0.19	
40	39	230/150	35.0	1.8	4.0	4.9	0.33	0.22	
41	65	200/130	71.0	2.6	6.1	..	0.33	0.20	
42	61	228/120	31.6	1.2	6.0	3.4	0.35	0.17	
43	47	240/130	26.0	1.1	4.0	4.7	0.25	0.19	
44	64	180/130	35.0	1.1	3.5	4.1	0.23	0.17	
45	50	200/100	43.0	1.2	4.3	6.0	0.24	0.20	
46	65	275/140	35.0	1.1	2.7	3.6	0.25	0.21	
47	60	160/94	40.0	1.1	2.5	3.6	0.27	0.21	
48	50	180/85	34.0	1.1	4.5	3.3	0.47	0.33	
49	16	170/120	60.0	2.7	5.5	5.3	0.49	0.39	
50	56	175/105	20.5	1.2	4.1	2.8	0.44	0.31	
51	57	186/105	33.3	1.2	5.0	4.0	0.50	0.33	
52	55	190/100	37.0	1.2	..	3.1	0.44	0.30	
53	42	180/90	35.3	1.2	..	5.6	0.30	0.30	
54	44	200/120	16.5	1.1	2.7	4.6	0.35	0.27	
55	52	234/146	42.0	1.3	3.0	3.5	0.36	0.31	
56	56	180/110	18.5	1.2	4.0	5.0	0.36	0.34	
57	63	180/100	54.0	2.0	4.8	6.4	0.33	0.23	
58	76	210/80	46.0	1.2	0.37	0.29	
59	60	196/126	31.6	1.2	4.0	4.0	0.29	0.12	
60	50	200/120	79.0	1.2	0.26	0.23	
61	54	190/120	52.0	1.3	..	12.5	0.21	0.06	
62	40	200/120	35.0	1.8	..	6.5	0.44	0.34	
63	62	178/80	31.6	1.9	..	4.4	0.29	0.23	
64	52	180/110	27.0	1.2	..	3.8	0.38	0.24	
65	60	190/110	26.1	1.1	0.39	0.22	
66	44	180/110	30.0	1.2	0.37	0.21	
67	54	200/120	35.0	2.6	0.38	0.18	
68	61	216/120	35.3	1.2	0.39	0.26	
69	80	170/90	46.0	1.2	0.27	0.13	
70	65	180/110	52.0	2.0	..	4.5	0.44	0.31	
71	56	180/100	53.0	1.3	..	3.5	0.16	0.10	
72	74	170/100	32.0	1.4	..	3.3	0.22	0.12	
73	63	180/110	21.0	1.2	..	5.2	0.20	0.06	
74	66	180/110	38.9	1.3	..	5.6	0.23	0.20	
75	56	165/110	35.0	1.1	..	4.4	0.21	0.15	
76	54	180/120	50.0	1.4	..	3.8	0.62	0.44	
77	43	180/120	37.0	1.3	..	1.5	0.43	0.30	
78	72	160/110	20.0	1.5	..	2.5	0.54	0.40	
79	39	175/130	35.0	1.3	..	4.2	0.51	0.20	
80	40	170/110	30.0	1.4	0.28	0.23	

* Blood chemistry in milligrams per 100 cc. of blood.

period when they had high blood "guanidin" values and then continued with a physiologic or adaptation hypertension after the primary cause had disappeared. Others may be examples of a different type of hypertension having a totally different set of etiologic factors.

Conclusion. The only positive statement we wish to make is that certain hypertensives show in their blood an increased amount of some substance giving the same color response as guanidin and having certain chemical properties like those exhibited by the guanidin bases.

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A STUDY OF THE BLOOD PRESSURE OF PATIENTS WITH DIABETES MELLITUS.

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BEFORE insulin was available most patients with diabetes died either of coma or of inanition. Insulin has made it possible for a new diabetic race to develop because with it such deaths can be avoided and, barring accident or incidental infection, the patients may live out their life expectancy. It is extremely important, therefore, to know whether or not diabetic patients are particularly likely to have hypertension.

Hypertension has been regarded by some authors as a significant complication of diabetes. Koopman said that in young patients blood pressure is normal, but in the older patients hypertension is the rule. Hitzenberger and Kylin found a large proportion of diabetic patients with hypertension. Katz-Klein found that the diabetes associated with hypertension is milder than the diabetes associated with normal blood pressure. Peterson found hypertension to be two and a half times as common in diabetic patients as in nondiabetic patients. Kramer recently studied 500 cases of diabetes, and concluded that hypertension in diabetics is "more common than we have been led to believe." One prominent American authority found an average systolic pressure of 139 mm. for diabetic patients of all ages; if this average had been "weighted" it would have been 148 mm. Rosenbloom, Elliott and others concluded that the blood pressure in uncomplicated diabetes is normal or slightly less than normal.

I have investigated the available material in The Mayo Clinic and have chosen 1001 diabetic patients for special study. Blood-pressure readings on these patients were obtained with a mercury manometer. The readings were made only after a period of rest in bed and were repeated by several observers.

Students of blood pressure have always deplored the lack of good controls. Most blood-pressure readings have been obtained from selected groups; the actual incidence of hypertension at various ages in the public at large has not been ascertained. Yet without this knowledge one cannot decide whether hypertension appears with greater frequency in any particular group of patients. Dr. W. G. Exton* has kindly supplied me with blood-pressure readings on a group of persons who applied for insurance. These data include not only readings of those accepted but of those rejected because of hypertension, and may be considered an estimate of the incidence

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of hypertension in the public at large, and this furnishes a control series which heretofore has not been available. The readings obtained in this group represent blood pressures of males and females ranging in age from fifteen to sixty years or more.

My cases were divided into two groups. In the first group all of the 1001 were included. In the second, cases of nephritis, hyperthyroidism, and arteriosclerosis were excluded. The weeding out of cases of nephritis and hyperthyroidism was not difficult. I cannot say with certainty that all cases of arteriosclerosis were eliminated. However, those were excluded with obvious sclerosis of the peripheral or the retinal vessels or with suggestive cardiographic changes or angina pectoris.

Obesity is considered by some as a contributory cause of hypertension. A previous study of the diabetic patients in The Mayo Clinic showed that 90 per cent were overweight and that 80 per cent were more than 10 per cent overweight at some time before diabetes began; 54 per cent were still overweight after having had diabetes for varying lengths of time. The weight factor in the diabetic patients whose records were used for the present study was corrected by determining the number of patients who were thin (more than 5 per cent underweight), normal (+ or -5 per cent) and stout (5 per cent or more overweight). By correcting the averages of various age groups on this basis, the weight factor was properly considered.*

Arbitrary standards were chosen for high-pressure and low-pressure groups. A patient of any age was considered to have a high blood pressure if the systolic pressure was more than 150 mm. or if the diastolic pressure was more than 100 mm. A patient of any age was regarded as having a low blood pressure if the systolic pressure was less than 110 mm. or the diastolic was less than 70 mm.

Table I shows that 16.2 per cent of the male diabetic patients have a systolic blood pressure more than 150 mm., as against 2.4 per cent of Exton's normal males; 26.7 per cent of the female diabetic patients have a systolic pressure more than 150 mm., as against 4.3 per cent of Exton's normal females.

Table II shows that 15.6 per cent of male diabetic patients have systolic blood pressure lower than 110 mm., as against 2.5 per cent of Exton's normal men; 19 per cent of diabetic women have systolic blood pressures less than 110 mm., as against 8.1 per cent of Exton's normal women. These data, like those of the high blood pressure group, are averages for all ages.

The advocates of the theory that high blood-pressure predominates in diabetic patients can point to Table I to support their

* The weight factor was corrected against a "control" group, which was made up of patients registering in the Clinic. This was the best material obtainable with all the necessary details for a weight correction. The build distribution (thin, normal or stout) was satisfactory, and the blood pressure did not vary much from the insurance averages quoted. The correction was done in the diabetic cases, and weighed against the blood pressure averages of the same groups in the control cases.

TABLE I.—PERCENTAGE OF CASES IN WHICH THE SYSTOLIC PRESSURE WAS MORE THAN 150, OR THE DIASTOLIC PRESSURE MORE THAN 100.

Cases.	15 to 19 yrs.	20 to 24 yrs.	25 to 29 yrs.	30 to 34 yrs.	35 to 39 yrs.	40 to 44 yrs.	45 to 49 yrs.	50 to 54 yrs.	55 to 59 yrs.	60 + yrs.	Total.
MALES.											
Systolic:											
Normal . .	0.6	1.6	0.4	0.9	1.0	1.8	4.4	6.3	9.4	21.0	2.4
Diabetic	4.5	25.0	6.0	30.4	32.5	22.0	16.2
Diastric:											
Normal	0.2	0.7	0.5	1.4	1.6	3.5	4.9	7.9	13.2	1.7
Diabetic	16.6	4.0	4.3	15.2	8.0	6.1
FEMALES.											
Systolic:											
Normal . .	0.5	...	0.4	1.3	5.2	5.8	14.5	12.3	25.0	33.3	4.3
Diabetic . .	16.6	10.5	21.0	12.1	32.0	35.0	39.0	43.0	26.7
Diastric:											
Normal	0.4	1.8	3.5	2.9	7.7	1.5	12.5	20.0	2.3
Diabetic	5.2	3.0	8.5	15.8	19.5	13.9	9.4

TABLE II.—PERCENTAGE OF CASES IN WHICH THE SYSTOLIC PRESSURE WAS LESS THAN 110, OR THE DIASTOLIC PRESSURE LESS THAN 70.

Cases.	15 to 19 yrs.	20 to 24 yrs.	25 to 29 yrs.	30 to 34 yrs.	35 to 39 yrs.	40 to 44 yrs.	45 to 49 yrs.	50 to 54 yrs.	55 to 59 yrs.	60 + yrs.	Total.
MALES.											
Systolic:											
Normal . .	7.6	3.4	2.8	2.1	2.3	2.1	2.2	0.7	2.5
Diabetic . .	18.2	23.1	24.0	31.5	39.2	12.5	14.3	16.7	15.6	5.7	15.6
Diastric:											
Normal . .	26.0	17.1	15.2	10.9	7.1	8.3	6.6	4.1	4.7	5.2	10.9
Diabetic . .	44.0	46.2	32.0	36.8	36.0	21.4	14.3	16.8	15.2	2.9	20.0
FEMALES.											
Systolic:											
Normal . .	15.3	13.1	10.5	7.1	4.0	1.4	1.6	1.5	3.1	3.3	8.1
Diabetic	17.6	27.6	27.3	...	12.5	4.4	4.0	5.3	3.4	19.0
Diastric:											
Normal . .	25.4	24.7	22.0	15.1	8.6	7.1	5.1	6.1	3.1	3.3	16.3
Diabetic . .	44.0	29.5	20.2	22.8	4.3	22.5	2.9	12.1	10.5	4.2	23.7

opinion. On the other hand, the proponents of the view that low blood pressure might be the rule in diabetic patients may find encouragement in Table II. The final "weighted" averages of Table III (Charts 1 and 2) do not disclose any significant difference between the blood pressure of diabetic patients and that of normal persons. The apparent contradiction between results, tabulated in Tables I and II may be explained by the wide "scatter" of the blood-

TABLE III.—AVERAGE BLOOD PRESSURE IN NORMAL PERSONS AND IN DIABETIC PATIENTS WITH AND WITHOUT HYPERTENSION—PRODUCING COMPLICATIONS.

Age.	Normal persons (5727).		Diabetic patients without arteriosclerosis, nephritis or hyperthyroidism (652).		All diabetic patients (1001).	
	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.
15 to 19	117.5±0.4	74.9±0.4	123.0±4.2	74.4±2.5	123.2±2.5	75.4±2.6
20 to 24	119.5±0.3	75.7±0.3	122.3±2.2	76.0±2.0	121.7±2.0	76.6±2.0
25 to 29	122.3±0.3	77.3±0.3	121.3±1.9	77.5±1.6	119.8±1.8	77.1±1.4
30 to 34	123.9±0.3	79.0±0.3	123.9±2.6	78.7±1.6	122.6±2.5	77.9±1.8
35 to 39	125.7±0.5	80.2±0.3	124.7±2.4	80.0±1.4	124.2±2.2	80.1±1.4
40 to 44	128.8±0.4	81.4±0.4	128.9±2.3	81.1±2.1	130.0±2.0	80.1±1.6
45 to 49	131.4±0.7	82.5±0.4	132.5±1.6	82.0±1.0	134.0±1.7	81.1±1.0
50 to 54	134.9±0.8	84.8±0.5	136.0±2.6	82.1±1.2	137.9±2.0	81.4±1.3
55 to 59	138.0±1.5	86.4±0.9	139.7±3.1	82.5±1.6	143.1±1.8	83.2±1.2
60+	141.3±2.0	87.4±1.4	141.1±2.1	82.6±1.2	144.0±1.4	84.1±1.8

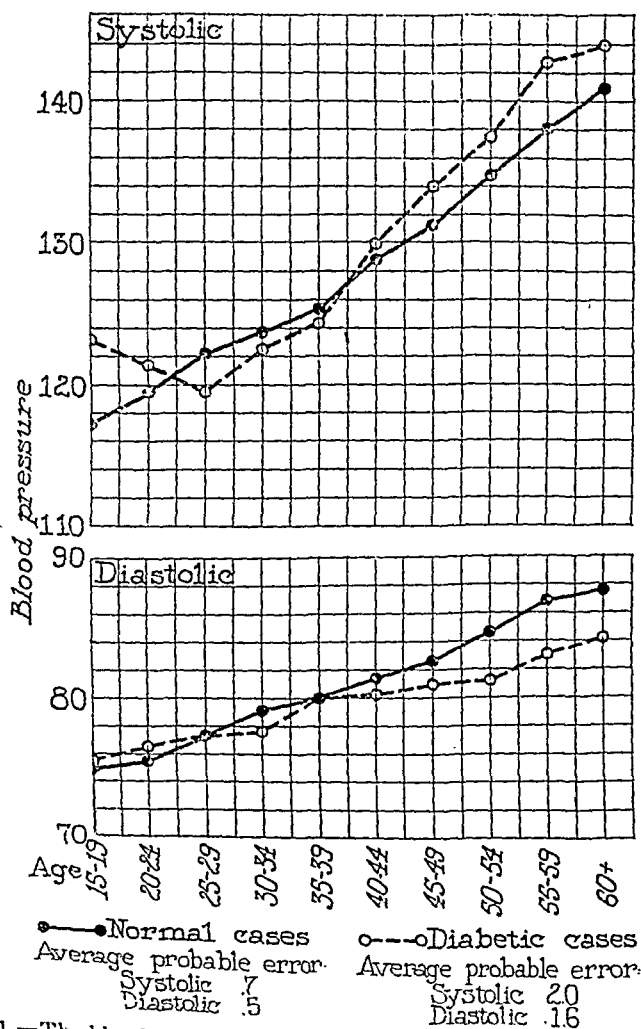


CHART 1.—The blood pressure of diabetic patients compared with the normal blood pressure.

pressure readings in diabetic patients as compared with the narrow scatter of blood-pressure readings of normal persons. The reason for the wide scatter is not clear; it may be due in part to an insufficient number of cases. There is, of course, a greater difference between the blood pressures of all diabetic patients and those of the normal group (Chart 1) than there is between the subgroups of patients who are free from nephritis, arteriosclerosis and hyperthyroidism, and the normal group (Chart 2).

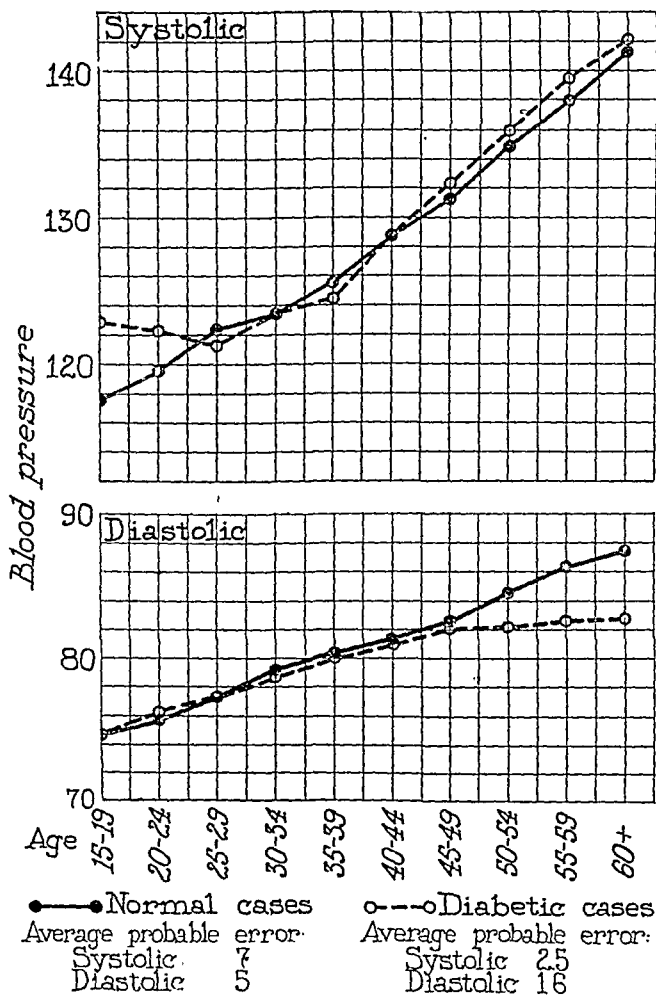


CHART 2.—The blood pressure of diabetic patients free from nephritis, arteriosclerosis and hyperthyroidism compared with normal blood pressures.

Uncontrolled diabetes particularly in the severer forms enforces a reduction of weight. Although adequate amounts of food are eaten, the food is not all metabolized and the result is the same as if a nondiabetic person ate a submaintenance diet. Weight reduction is an important measure in treating diabetes. Weight loss, therefore, is an important factor in cases of treated and untreated diabetes alike. Benedict, in his study of the effects of restricted

diets on a group of young men, found among many other significant facts a definite lowering of the systolic and diastolic blood pressure. The blood pressure of Benedict's fasting man became lower as the fast continued.

From the foregoing one is led to believe that the blood pressure of diabetic patients might be higher if the element of weight loss did not enter into consideration. In this study the results tabulated in Table I might, therefore, approach the truth much more closely than the results shown in Table II. If the figures in Table II can be discounted it would mean that diabetic patients as a class were more susceptible to hypertension than normal persons. On the other hand, several points with reference to these cases should be considered: (1) Prolonged undernutrition in treated and untreated cases would be more common in the younger patients. The younger patients form but a small part of the whole group. (2) In many instances the patients did not lose much or any weight until treatment was started and the blood-pressure readings used in this study were those obtained soon after admission to the hospital. (3) Corrections for weight were made against a group of routine patients coming to the Clinic, and this group included patients who had lost weight, as well as those who had gained.

Summary. Heretofore students of this problem have usually considered only half of the picture, that is, they have considered only the high pressures. In this way one finds that there are more diabetic patients than there are normal persons with systolic pressure of more than 150, and from this fact alone one might conclude that diabetic patients are more likely to have hypertension than normal persons of comparable age groups (Table I). On the other hand, a similar analysis of those with low pressures shows that more diabetic patients have a systolic pressure less than 110 than normal persons of comparable age groups. One might conclude from Table II that hypotension is more common in diabetic patients than in so-called normal persons. If, however, the high and low pressures of diabetic patients, and of normal persons are averaged, a significant difference is not found (Table III and Chart 2).

Conclusions. An analysis of the blood pressure of the diabetic patients seen in The Mayo Clinic does not provide clear evidence to show that diabetes of itself promotes hypertension. If the blood pressure of diabetic patients is elevated it suggests the presence of some associated abnormality which of itself is responsible for the hypertension.

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AN EXPERIMENTAL STUDY OF THE INFLUENCE OF FERRO-MAGNETIC CUBIC AND PARAMAGNETIC AMORPHOUS IRON OXID ON THE BLOOD.

(IN SIMPLE ANEMIA AND IN THE NORMAL.)

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It is now recognized that there is a normal iron reserve in the tissues of the healthy body available for the building up of hemoglobin. The need for iron in some types of clinical anemia may be explained, in part at least, by the depletion of this reserve. The fundamental studies of Whipple¹ and his associates in experimentally controlled anemias have laid the foundation for an ultimate understanding of the many factors involved. In the simple anemia following brief periods of hemorrhage Hooper, Robscheit and Whipple found that medicinal iron did not hasten or increase the regeneration of hemoglobin. This observation has been repeatedly confirmed by many others^{2,3} using the oral, subcutaneous and intravenous routes for administration of various iron salts. However, Whipple and Robscheit-Robbins did find in their dogs that, in the presence of a long continued, severe anemia due to repeated hemorrhages, iron in the form of Bland's pills had beneficial effects, though never so striking as those obtained with the feeding of liver. Riecker⁴ has recently emphasized the depletion of available iron after prolonged hemorrhage, particularly as it is related to the synthesis

of hemoglobin in distinction to cell regeneration, and urges the efficacy of iron therapy (ferric citrate and ferrous carbonate) in the treatment of this type of anemia. In as much as iron may be inactive in some anemias and quite potent in others the mechanism of this reaction is not simple, and it may very well include factors other than that involving a mere attempt at replacement of iron necessary for the hemoglobin molecule.⁵

Utilizing the nutritional anemia in rats, Mitchell and Vaughn⁶ have made an extensive comparative study of the relative availability of different forms of iron, as evidenced by the hemoglobin response. They found that the addition to the diet of small amounts of ferric citrate, ferric albuminate, ferric chlorid, and ferric acetate apparently produced good results; peptonized ferric oxid, saccharated ferric oxid, saccharated ferrous carbonate and ferrous iodid gave only fair improvement; while ferric oxid, ferrous carbonate, ferric potassium tartrate, ferrous lactate, ferrum reductum and ferrous sulphate all yielded poor results. They emphasize the relationship of solubility of the iron salt to its efficacy and the advantage in general of the ferric over the ferrous forms. Hart and his coworkers⁷ found that in the nutritional anemia induced in rabbits by an exclusive diet of whole milk, inorganic iron in the form of Fe_2O_3 was ineffective; but when in addition to the iron oxid, fresh cabbage, or an alcoholic extract of dried cabbage, or the ash of cabbage or lettuce was used, the anemia was prevented. They also found that the anemia following the whole milk diet could be prevented by another form of iron, namely, impure soluble $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$. The question of the relative merits of ferrum reductum, ferric and ferrous iron seems still to be a debatable one.

With the discovery of a ferromagnetic cubic form of iron oxid by Welo and Baudisch,⁸ followed recently by the advocacy of its use therapeutically under the trade name of "siderac" in the German literature, it has seemed desirable to analyze its effect under the controlled conditions of a simple anemia. Through the generous coöperation of Dr. Baudisch we have had at our disposal chemically pure ferromagnetic iron oxid (Fe_2O_3) and the paramagnetic amorphous iron oxid ($\text{Fe}_2\text{O}_3 \cdot x\text{H}_2\text{O}$) prepared by him. This new amorphous iron oxide ($\text{Fe}_2\text{O}_3 \cdot x\text{H}_2\text{O}$) is different from the rhombohedral, inactive iron oxid (Fe_2O_3), which was prepared from its cubic ferromagnetic form.* These substances were put up in gelatin capsules, each containing 3 mg. of the ferric oxid triturated with sugar of milk 1 to 10. Rabbits were employed for the experiments. The iron was administered by mouth in doses of either 3 or 6 mg. per day, in rabbits ranging from 1800 to 2800 grams in weight. This is on the basis of a dosage of 100 to 200 mg. for the adult human.

* The amorphous paramagnetic iron oxid has been prepared in an entirely new way. The method of preparation will be given in another journal.

Ferromagnetic Iron Oxid. Rabbit R429 (Chart I) was bled four times from the heart at forty-eight-hour intervals, which reduced the red cells from 6,100,000 to 3,250,000 (February 21, 1928) and the hemoglobin from 67 per cent (Newcomer) (11.33 gm. per 100 cc. blood) to 42 per cent (February 23, 1928) (7.10 gm.). On the sixth day after the last bleeding, the total count of the red cells had returned to 5,310,000, hemoglobin 60 per cent (10.15 gm.), and on the sixteenth day the count reached 6,500,000, hemoglobin 65 per cent (10.99 gm.). The original color index was 0.54; at the time of greatest anemia it was 0.73; on reaching 5,310,000 cells, it was 0.56; with 6,500,000 cells, 0.50; and twenty-two days after the original bleedings, when the red blood cells were 5,380,000 per c.mm., the hemoglobin (color index 0.62) had returned to its original level of 67 per cent (11.33 gm.).

The same rabbit was again bled from the heart on successive days, until the red cells were only 3,070,000 and the hemoglobin 36 per cent (6.09 gm.), color index 0.58. At this time the administration of ferromagnetic iron oxid, 6 mg. per day by mouth, was started. Again the 5,000,000 point was regained on the sixth day with the hemoglobin 54 per cent (9.13 gm.) and color index 0.54; but this level was not maintained. The majority of

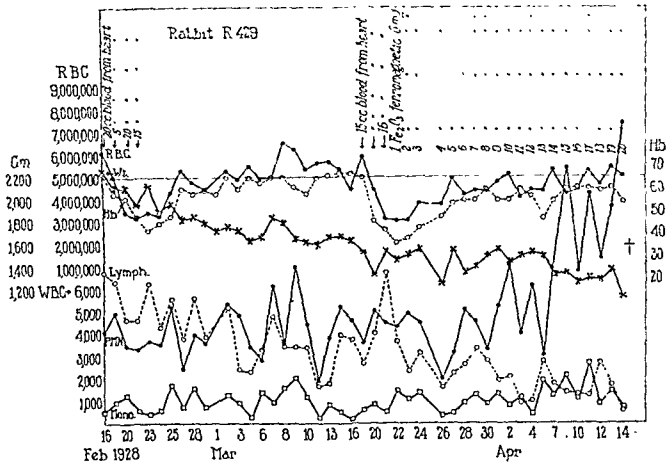


CHART I.—Studies of the blood of Rabbit R429.

the counts thereafter remained between 4,000,000 and 5,000,000, with the hemoglobin fluctuating between 47 per cent (7.95 gm.) and 60 per cent (10.15 gm.), and color index between 0.53 and 0.64, with a final in dex of 0.54. The differential count of the white cells was not remarkable, except for the terminal rise in neutrophilic leukocytes. There was a gradual loss in weight from 2200 gm. to 1125 gm. during the period of observatio n. This animal died on the twenty-third day after the iron was started. Asⁱde from some small patches of bronchopneumonia in the right upper lobe of the lungs, accounting for the leukocytosis, there was no obvious cause of death at autopsy. The spleen weighed only 0.4 gm., a decrease proportional to that of the body weight, and it showed no hemopoiesis. The bone marrow of humerus and femur was very elastic, gelatinoid, granular, mottled, and grayish-brown in color. The distal end of the tibia, usually acellular and fatty, showed no hemopoiesis. Histologically, the red cells seemed distinctly decreased in relative and absolute numbers. The majority of the red cells were late erythroblasts with only a few younger cells and normoblasts. Sabin and Doan⁹ have found the normoblasts to constitute 69 per cent of the nucleated red cells in the marrow of normal rabbits. There was also a definite shift to the left in the myeloid series, myelocytes "C" being

markedly outnumbered by the "B" myelocytes, whereas the normal percentage of myelocytes "C" is 85 per cent.⁹

Under the administration of ferromagnetic iron oxid, then, this rabbit, during equivalent periods of observation after a simple anemia, averaged a return in the red cells to a level approximately a million less than that attained on a normal diet without iron, and the hemoglobin averaged 0.85 gm. to 1.7 gm less. If the normal iron reserve was depleted during the first period of regeneration of red cells, then the iron subsequently given was unable to replace this store. For, though the total cells had returned at the end of three weeks in each case to approximately the same level, the hemoglobin was 7 to 10 per cent less on the second recovery, making the difference in color indices 0.62 and 0.54 respectively.

To test whether an iron depletion during the first recovery from bleeding (Chart I) had to do with the slower recovery with the iron after the second bleeding, Rabbit R423 was bled from the heart on six occasions at forty-eight hour intervals, which reduced the red cells from between 5,000,000 and 6,000,000 to 3,000,000. The hemoglobin dropped from about 70 per cent (11.84 gm.) to 39 per cent (6.59 gm.), and the color index changed from 0.59 to 0.62. The daily administration of 3 mg. of ferromagnetic iron oxide by mouth was started at once. In 3 control rabbits rendered anemic and permitted to regenerate cells under the conditions of a normal, adequate, herbivorous diet, the original level of red cells was regained on the sixth, eighth and tenth days, and the hemoglobin on the tenth, eighth and tenth days respectively. In Rabbit R423, on the other hand, the original level of red cells was not reached until the sixteenth day, and that of the hemoglobin not until the twentieth day. The differential count of the white cells was not unusual and there was a well-maintained weight curve. The color index at the end of twenty-two days was 0.65.

Now the iron was discontinued for nine days and a second series of four cardio-punctures, at twenty-four-hour intervals, was carried out, reducing the total red cells to 2,700,000 and the hemoglobin to 33 per cent (5.58 gm.). This time 6 mg. of ferromagnetic iron oxid were given as the daily dose. Again there was a strikingly prolonged period of recovery, the total red cells first reaching the 5,000,000 mark on the sixteenth day of treatment, but with the average count remaining well under this level until after the iron was stopped at the end of twenty-one days. The hemoglobin, too, remained under 60 per cent (10 gm.) for this entire period. There was some loss of weight during the second period of observation.

Ferromagnetic iron oxid, under the conditions of the experiment, did not merely fail to aid in the regeneration of hemoglobin after simple anemia, but seemed actually to delay the return to the normal. In view of this latter finding, tests were carried out of its effect on the blood condition in normal rabbits.

Rabbit R304 (Chart II) was followed over a period of six months with complete blood studies at weekly intervals. During this control period the red cells remained above 6,000,000 for the most part, the cells and hemoglobin reaching 7,000,000 and 85 per cent (14.38 gm.) respectively just prior to the initiation of the iron therapy. There had been a gradual increase in weight during the six months, from 2000 gm. to 2700 gm. Ferromagnetic iron oxid, in daily doses of 6 mg. by mouth, was begun. During the succeeding two months in which it was regularly given, there was a gradual but steady decline in the red cells to a low point of 4,380,000, accompanied by a fall in the hemoglobin to 63 per cent (10.65 gm.)—an

average decrease of 1,500,000 to 2,000,000 cells and an average fall of more than 15 per cent (2.5 gm.) of hemoglobin (maximum fall 22 per cent—3.72 gm.). Instead of a steadily rising weight curve there was, after the iron was started, a decrease in weight. The white blood cells maintained their usual relative proportions.

Fifty-seven days after the iron was begun, this animal was killed by air embolism and autopsied. There was nothing unusual in the tissues or organs in the gross, except in the bone marrow. On surveying the marrow of the several long bones, it was clear that there was quantitatively less active hemopoietic tissue in them than is found in the normal rabbit. The femoral marrow on both sides was mottled with foci of fat, there being one area of about 1 cm. in extent, just proximal to the middle of the diaphysis, entirely fatty, whereas under normal conditions it is usual to find this cavity filled with red marrow. Both humeri showed areas of fat near the distal ends of the bones; the distal ends of both tibiae and the entire extent of both radii and both ulnae were yellow fat, and this in the presence of a falling red-cell count. The gross appearances were confirmed histologically.

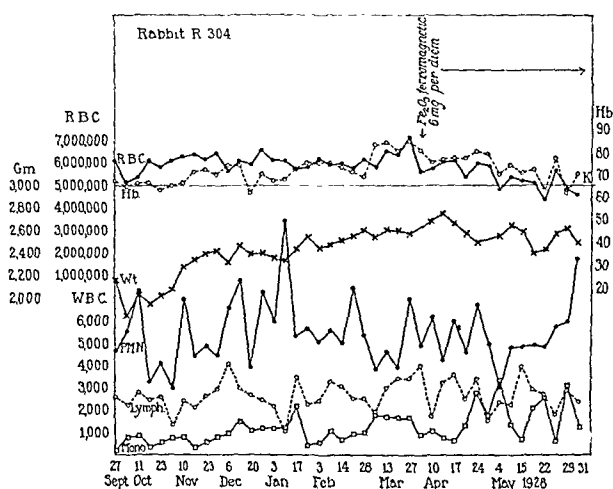


CHART II.—Studies of the blood of Rabbit R304.

The fat was extremely unevenly distributed in the marrow, some areas showing nothing but enormously distended fat cells, in contrast with other areas, where the fat was in a finely divided state. There was a marked increase in the clasmatoocytes, all being filled with phagocytized, yellowish-brown pigment, such as is encountered under circumstances of abnormal blood destruction. A differential count of representative preparations, from which 2000 cells were counted, resulted as follows: Myeloid cells 48 per cent, erythroid cells 48.2 per cent, clasmatoocytes 1 per cent, primitive cells 2 per cent, lymphocytes 0.25 per cent, monocytes 0.05 per cent. The myeloid-erythroid ratio was thus 48 to 48.2, whereas for the bone marrow of normal rabbits it is 70 to 25.⁹ Of the nucleated red cells, 51 per cent were normoblasts, 35 per cent late erythroblasts, 13 per cent early erythroblasts, and 0.04 per cent megaloblasts. This is in contrast to the average of 5 normal rabbits, as given by Sabin and Doan:⁹ Normoblasts 69 per cent, late erythroblasts 26 per cent, early erythroblasts 4 per cent, and megaloblasts 0.04 per cent.

It is evident that the total extent of blood-forming tissue was so reduced in Rabbit R304, and the percentage of available normoblasts so decreased,

as contrasted with other stages of nucleated red cells, that the relative increase in erythroid to myeloid tissue was insufficient to maintain the original level of red cells in the peripheral blood. The spleen showed no compensatory hemopoiesis.

The experiments appear to show that the administration of ferromagnetic iron oxid not only fails to aid in the regeneration of blood during a simple anemia but actually causes anemia in normal animals. In four experiments with this form of iron the results have been consistent.

Amorphous Iron Oxid. Three experiments with controls to correspond were carried out with the amorphous iron oxid. In Rabbit R422 (Chart III)

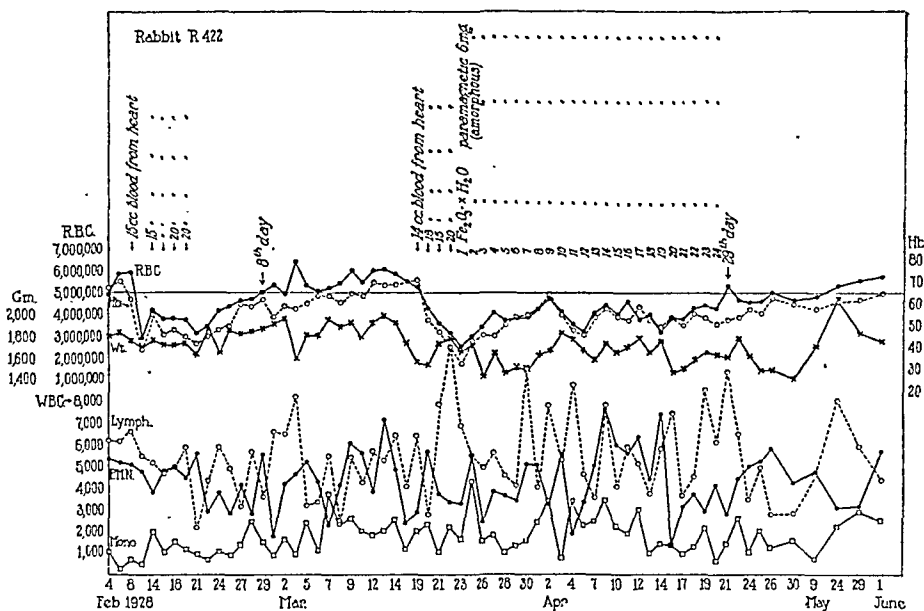


CHART III.—Studies of the blood of Rabbit R422.

the red blood cells were reduced from between 5,000,000 and 6,000,000 to 3,200,000 by a series of five cardiopunctures, the hemoglobin falling from between 60 per cent and 70 per cent (10 and 12 gm.) to 42 per cent (7.10 gm.). By the eighth day, the red cells had returned to 5,000,000 with hemoglobin 62 per cent (10.49 gm.) and color index 0.62 (original color index 0.67). The red cells and hemoglobin continued to maintain their normal range of fluctuation as originally determined until a second series of bleedings from the heart again reduced the red cells to 2,600,000 and the hemoglobin to 33 per cent (5.58 gm.), color index 0.63. At this point a daily dosage of 6 mgm. of amorphous iron oxid, paramagnetic, by mouth, was begun. During a period of time similar to that of the first observations, twenty-eight days, the red cells never returned to 5,000,000, averaging between 3,000,000 and 4,500,000 for the most part. The percentage of hemoglobin paralleled closely the total count, ranging from 46 per cent (7.78 gm.) to below 60 per cent (10 gm.), except for one reading of 65 per cent (10.99 gm.). Following the stopping of the iron by mouth, both red

cells and hemoglobin showed a tendency to increase to the original level of above 5,000,000 and 10 gm. hemoglobin. Whereas after the first bleedings the total red cells had returned to 5,000,000 on the eighth day after the last hemorrhage, after the second series they did not reach this until the twenty-ninth day, and then only after the cessation of the iron. The hemoglobin per red cell was slightly more than in the original period of observation, the color indices ranging from 0.71 to 0.65, so that the depressant effect was primarily one on the replacement of cells. There was a decided increase in body weight after the iron was discontinued. The white cells showed a consistent lymphocytic predominance, as happens in certain rabbits, with an occasional rise in monocytes, but otherwise nothing remarkable.

A similar experiment, but with the order reversed, was carried out in Rabbit R430 (Chart IV) to control the preliminary depletion of iron as a

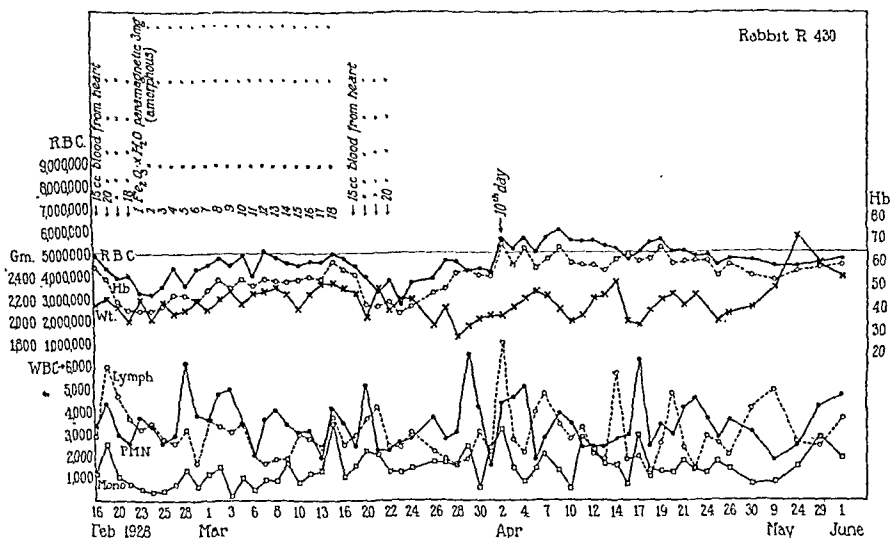


CHART IV.—Studies of the blood of Rabbit R430.

possible explanation of the second delay in regeneration of red cells. After reducing the red cells by repeated cardiopunctures to 3,200,000 and the hemoglobin to 40 per cent (6.76 gm.), 3 mg. of amorphous iron oxid were given daily. The red cells first passed the 5,000,000 mark on the thirteenth day thereafter, and the color index reached 0.52, though it was not maintained at this level. The hemoglobin did not rise to 55 per cent (9.3 gm.) until the nineteenth day. The iron was stopped after twenty-two days (18 doses), when the color index was 0.60, and after an interim of five days the red cells were again reduced through repeated bleeding from the heart. From a low point of 2,800,000 red cells, with hemoglobin of 39 per cent (6.59 gm.) and color index 0.69—a lower absolute level than that obtained in the previous observation—the count rose to 5,700,000 by the tenth day, hemoglobin 70 per cent (11.84 gm.), color index 0.61, with the level maintained.

In this instance it seems clear that the administration of 3 mg. daily of the amorphous iron oxid retarded the return to normal in both red cells and hemoglobin and prevented the overcompensation seen on chart IV after the second bleeding.

Rabbit R112 was followed by means of complete blood studies at weekly intervals from October, 1926, to April, 1928. The red cells throughout this period remained above 6,000,000, with the exception of a very occasional count of between 5,500,000 and 6,000,000. The hemoglobin ranged between 75 per cent (12.69 gm.) and 90 per cent (15.22 gm.), reaching a high point of 97 per cent (16.41 gm.) on April 3, at which time 6 mg. of amorphous iron oxid daily by mouth were started. During the following two months both red cells and hemoglobin showed a decline to low points of 4,900,000 and 69 per cent (11.67 gm.) respectively, a fall of between 1,000,000 and 1,500,000 in cells and of 28 per cent (4.74 gm.) as a maximum for the hemoglobin.

Here again in the normal rabbit the initiation of iron oxid therapy by mouth produced a definitely depressant effect.

Summary. In general, these observations tend to indicate that both the ferromagnetic iron oxid (Fe_2O_3) and paramagnetic iron oxid ($\text{Fe}_2\text{O}_3 \cdot x\text{H}_2\text{O}$) act similarly in their effect on hemopoiesis in the rabbit both in the normal state and in that of a simple anemia after hemorrhage. The magnetic property apparently exerts no significant biological effect.* The emphasis has been placed heretofore upon the presence or absence of a beneficial effect in considering the various iron salts in blood deficiencies. The studies here reported direct attention toward the possibility of a positively unfavorable effect, a definite depression of hemopoiesis, attending the administration of iron in certain forms.

From this brief report of the effect of ferromagnetic and paramagnetic iron oxid in the normal rabbit and in rabbits suffering from a simple anemia after hemorrhage, it is suggested that this treatment in clinical cases of secondary anemia may be a disadvantage and should not be undertaken without further experimental data.

* An observation which may be significant in this connection was made by Welo and Baudisch;⁸ they found that ferromagnetism and catalytic activity in iron oxid have no essential relationship.

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THE TREATMENT OF SPRUE WITH LIVER EXTRACT (343).

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IN a previous note¹ we reported the results of treatment of a patient with sprue by the high-liver diet of Minot and Murphy. The rationale of the procedure was based on the similarity of sprue and pernicious anemia. The case, in brief, concerned itself with a man, aged forty-three years, seen in the summer of 1927, who had gone to the Philippines in 1924 and returned to this country in 1926. For fourteen months there had been continuous diarrhea with huge, pale, frothy stools, attacks of stomatitis and general debility. There was moderate anemia with high color index, leukopenia, anisocytosis and poikilocytosis and many large cells. Within a week after starting the liver diet the bowels were almost normal and there was a rise in reticulocytes to 6 per cent followed by improvement in the red-cell count. Within two months the patient left the hospital feeling perfectly well, having gained 25 pounds. The bowels were practically normal and the blood count showed over 5,000,000 red cells with 100 per cent hemoglobin.

The present report deals with 2 further cases of sprue in which satisfactory remissions were obtained by the use of Liver Extract 343 (Lilly).

Dietetic Treatment of Sprue. All the accounts of sprue abound in dietary suggestions: the milk cure, the strawberry cure, the banana cure and the water-meat cure may be mentioned as examples. The details of regimen vary with the experience of different observers. It is quite clear, however, that none of these methods of treatment have possessed any reliable degree of effectiveness, and many of the good results may be explained by "spontaneous" remissions which are common in sprue as well as in pernicious anemia. While liver is mentioned occasionally as being beneficial (especially in the form of liver soup) we can find no accounts of adequate liver feeding in sprue in the sense in which it has been carried out in pernicious anemia. Occasional statements that liver is actually harmful may also be found.²

Relation of Sprue to Pernicious Anemia. As we said above, the intensive use of liver in the present series of cases was suggested by the similarity of sprue and pernicious anemia. The question of the relationship of the two diseases and their possible identity has been thoroughly discussed in the recent literature,³ but the matter

does not seem to be finally settled. Ashford's studies on *Monilia* seemed for a time to favor a specific etiology in sprue; but Nye⁴ has recently found yeasts in both sprue and pernicious anemia and brings forward good evidence that they are secondary invaders in both conditions. Central-nervous-system changes are said to be less common in sprue than in pernicious anemia and the typical "sprue stool" is certainly not often seen in the latter; however, these are not absolute distinctions. We have been impressed by the undoubted presence of considerable amounts of free hydrochloric acid in the gastric secretions of the cases herewith reported. If, as most observers feel, anacidity is an essential feature of pernicious anemia, one would seem to be dealing with a different condition. At any rate, until the specific cause of both diseases is discovered they may well be regarded as distinct clinical entities.

Case Reports. CASE I.—J. S., aged twenty-five years, an American mechanic, entered the hospital on February 29, 1928, complaining of pain in the stomach, diarrhea, weakness and bloody urine.

The past history seemed unimportant except for the fact that he had been in the Philippines from 1924 to 1927 in the army. His previous health had been good.

In 1925, and again in 1926, he had brief attacks of diarrhea, featured by gaseous distention of the abdomen and passage of huge pale, frothy stools. There were cramps and tenesmus. In December, 1926, the diarrhea recurred and persisted up to the time of entry. The patient stated that there had been five or six movements daily and he estimated the usual size of the passage as "about a gallon." There had also been frequent attacks of "sore burning mouth." At about the time of onset of the diarrhea he began to pass bloody urine. This was very marked at times and was still present on entry. There had been great loss of weight.

On examination he seemed extremely ill, prostrated and very pale. There was marked papillary atrophy of the tongue which appeared red and raw. There was a systolic murmur at the apex and the pulse rate was 120. The abdomen was distended and tympanitic. The liver and spleen were not felt. No definite neurologic changes were discovered. The blood count was: red blood cells, 740,000; hemoglobin, 25 per cent (Sahli); leukocytes 2500; polymorphonuclears, 39 per cent; lymphocytes, 56 per cent. There was marked anisocytosis and poikilocytosis and moderate diffuse basophilia. The urine was brownish-red and contained innumerable red blood cells. There was much albumin, but no casts were seen. The stools were pale yellow, foul and extremely bulky. They contained a large amount of fat; there was no blood, pus, mucus or parasites, but there were many yeasts. Gastric analysis after histamin showed a maximum ten-minute secretory volume of 26 cc. with free HCl 105 and total acid 111. Scrapings from the tongue yielded *monilia*.

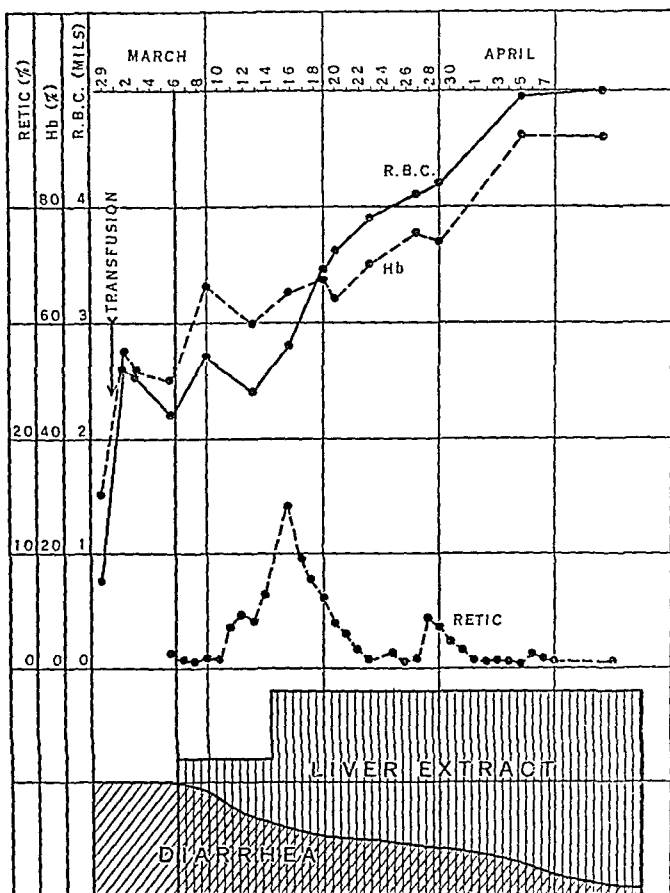
An investigation of the urinary tract by Dr. Dillon showed a urethral stricture and injection and varicosities of the bladder wall, which were evidently the source of the bleeding. On March 1, a suprapubic cystotomy was done and a periurethral abscess was incised. After suprapubic drainage was established the urine gradually cleared up. The wound was closed later and when the patient left the hospital the urinary tract was in normal condition.

On March 1, a transfusion of 600 cc. of citrated blood was given as a preliminary to the operation. That this played no apparent part in the sub-

sequent course is suggested by the fact that the blood count was falling when liver extract was first given. The effects of the liver therapy are shown in Chart I. Aside from the extract, equivalent to 400 to 600 gm. daily, treatment consisted of bedrest, liberal diet without liver and symptomatic measures.

The response to liver was clean cut in spite of the fact that at first there was still considerable loss of blood in the urine. On the fourth day of treatment he began to feel better, it was less difficult to eat, the stools became less bulky and the abdominal cramps and sore mouth improved. Progress

CHART I.



was uninterrupted and the patient left the hospital thirty-seven days after the liver treatment was begun. The red cells had reached 5,000,000; there had been a gain of about 30 pounds in weight. There were one or two soft or formed brownish stools daily which still contained, however, an excess of fat. He felt perfectly well.

In summary, then, a patient with sprue with marked diarrhea, stomatitis, emaciation and anemia, complicated by urethral stricture and hematuria, responded remarkably to liver extract and within five weeks was symptomatically well.

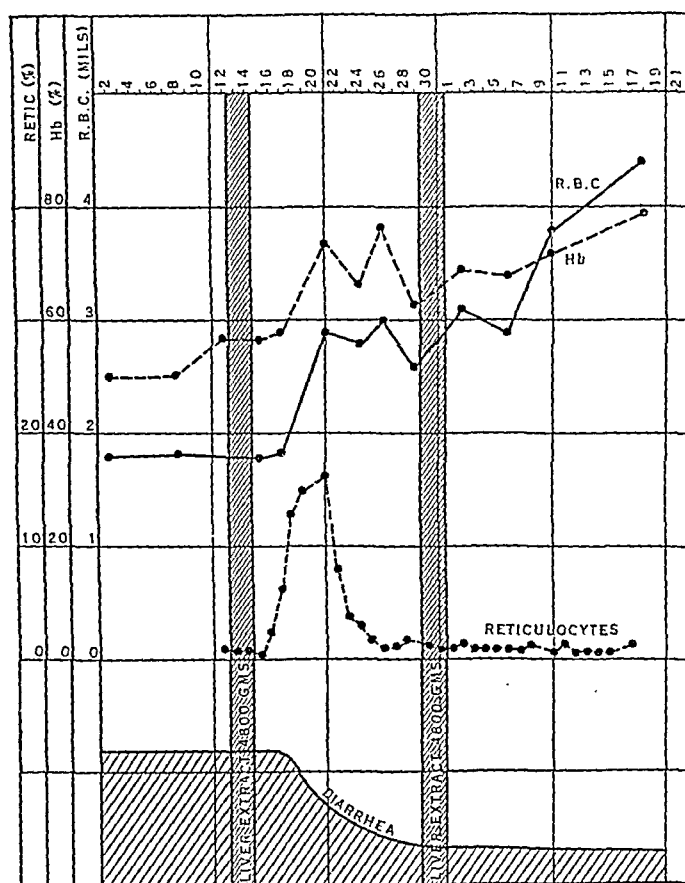
CASE II.—J. G., a Spanish laborer, aged fifty-seven years, entered the hospital February 27, 1928, complaining of nausea, gas on stomach and diarrhea of three years' duration.

The past history seemed unimportant except for the fact that for ten years there had been some gas and discomfort after heavy meals.

Three years ago he began to have three to five loose bowel movements daily associated with moderate abdominal discomfort. He had lost 26 pounds and has felt generally run down. His habits are not remarkable and he has been in the United States for the past twenty years.

On entry he looked sick and worn. There was moderate undernutrition (weight 52 kg.) and marked pallor without distinct yellowish tint. The tongue showed papillary atrophy with redness of the margins but no ulcerations. The liver and spleen were not felt. No neurologic changes were made out. The remainder of the physical examination showed nothing abnormal.

CHART II.



The blood count on entry was: red blood cells, 2,000,000; hemoglobin, 50 per cent; leukocytes, 4000; polymorphonuclears, 50 per cent; lymphocytes, 40 per cent. There was marked anisocytosis and poikilocytosis and many macrocytes were present. The stools were moderately bulky, light yellow, soft and pasty, with much fat. Monilia were present, but no parasites. The stools at first numbered two to five per day. Gastric analysis showed free HCl, 23; total acid, 34. After histamin, the ten-minute secretory volume was 17 cc. The free HCl reached 60, and the total acid 70.

It was evident that the patient fell into the general group of sprue or pernicious anemia. In view of the character of the stools and the presence of free HCl, the former seemed the most logical diagnosis. It was decided to try the effects of large doses of liver extract, given over a brief period of time. The patient was kept in bed on a liberal general diet without liver and on March 13 and 14, liver extract (343); equivalent to 4800 gm. of

liver, was given in divided doses. There were no untoward effects. The results are shown graphically in Chart II. On the third day a typical reticulocyte response began followed by a rapid rise in the red-cell count. Three days after the liver feeding there was marked subjective improvement and the stools became fewer in number. The tongue papillæ returned rapidly. Improvement thereafter continued steadily. On March 28 there was a slight drop in the blood count and another large dose of extract was given. This, as might have been expected,⁵ elicited no reticulocyte response, but was followed by still further gain in blood count. The latter part of his hospital stay was complicated by a perirectal abscess which required surgical drainage. In spite of this, he left the hospital less than five weeks from the beginning of treatment feeling well and with a red cell count of nearly 4,500,000. There were only one or two brown semiformal stools daily, but there was still an excess of fat.

Discussion and Summary. The results of treatment, by liver extract, of 2 cases of sprue are reported. The diagnosis of sprue as against pernicious anemia was based on the presence of considerable amounts of free HCl in the stomach juice, the character of the stools, the absence of neurologic changes and (in 1 case) residence in the tropics. Responses similar to those usually obtained in pernicious anemia resulted, with rise in reticulocytes, increase in blood count and improvement of gastrointestinal symptoms with gain in weight and general well-being. Incidentally, it has been pointed out that the typical response may be obtained after a single large dose of liver extract as well as after daily smaller doses. The results are additional evidence of a close relationship between sprue and pernicious anemia.

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COINCIDENT DIABETES MELLITUS AND PERNICIOUS ANEMIA.

WITH REPORT OF A CASE.

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REPORTING in 1926 the discovery of gastric achlorhydria or subacidity in a large proportion of their diabetic patients, Bowen and Aaron¹ comment upon the extreme rarity of coexisting diabetes and primary anemia. Further, a review of the literature which I under-

took in connection with the study of the case presented below revealed only 6 case reports in which the individual was considered to have had both diseases simultaneously. The findings set down by the various authors will be summarized for comparison with the present case.

Review of Literature. Claude Bernard² first showed that hyperglycemia may result from repeated bleedings of dogs, yet experimental work on the interrelation of blood quality and pancreatic hormone seems not to have been carried further.

The earliest adequate case report found was that of Parkinson,³ who in 1910 published the record of a man who came under his observation with a year's history of symptoms referable to pernicious anemia. Full physical and laboratory data indicated a well-advanced stage of the disease. Glycosuria was not present. The patient proceeded to enter upon a remission under a regime including high-protein, high-caloric diet, hydrochloric acid and arsenic. Five months later he was readmitted to the hospital with ten days of symptoms of profound anemia and of diabetes. Urinalysis showed 5 per cent sugar, later increasing amounts of acetone bodies; and the patient died five days after entry. At necropsy the pancreas was described as small, but normal microscopically; the bone marrow changes as typical of Addisonian anemia. The author expresses "little doubt that the diabetes followed on a relapse in the primary anemia," but that no anatomic changes were found to account for it.

Parkinson, speculating on the possible relation between anemia and diabetes, searched the literature to find an explanation for the low incidence of the diabetic syndrome in the face of the diminished oxygen-carrying capacity of primary anemia blood. He was able to find, he states, no mention of it in the general literature, nor "in the monographs of Addison, Byrom Bramwell or Hunter. And none in the articles of Cabot, von Noorden or French in the *Systems of Medicine*."

In a treatise on the diseases which may be associated with Addisonian anemia, Giffin and Bowler,⁴ reviewing 628 anemia cases with 108 complicating diseases, mention diabetes mellitus as one such complication. Two of their anemia patients showed disturbed sugar metabolism. In one, polyuria and a blood sugar of 0.27 per cent developed; in a second instance, transient glycosuria was found. These authors, too, mention the fact that glycosuria, if not true diabetes, may be secondary to anemia, possibly as a result of a deficient oxygen supply.

A third instance of the association was furnished by Schumann⁵ who detailed the findings in a woman, aged fifty-five years, who had pernicious anemia. In this patient, the central nervous system symptoms were marked: insomnia, girdle sensation, tingling and numbness of hands and feet. In addition, routine urinalysis showed a large amount of sugar; blood sugar was 0.222 per cent. The

blood Wassermann test was negative. The hemoglobin was 35 per cent; erythrocytes, 1.2 millions; leukocytes, 6400; the stained film showed much anisocytosis and poikilocytosis. There was no evidence of bleeding in the gastrointestinal tract.

With exclusion of foods containing sugar, and a daily small dose of insulin, the patient's glycosuria disappeared in ten weeks. Subsequently, sugar-containing foods were permitted without recurrence of the diabetes. The anemia picture "ran the usual course," and transfusions were given for a time. The report does not mention gastric acid findings or remissions in the anemia.

Two of the 3 cases reported recently by Adams⁶ were particularly clear-cut. One patient, a woman, aged forty-five years, was first diagnosed as anemic in 1912. Symptoms were indefinite, findings suggested splenic anemia. She was followed fairly closely until 1923, during which years the spleen remained enlarged. In that year, 8.2 per cent of urinary sugar was discovered, the first suggestion of diabetes. The latter was easily controlled, however, without insulin, and did not interfere with removal, early in 1923, of hemorrhoids which had bled intermittently. Paresthesias appeared in December, 1923, and a month later, the patient was found on readmission, to have a severe anemia of the Addison type, along with hyperglycemia. The hyperglycemia was removed with insulin, and she went home, where she gave up insulin, and returned two months later in diabetic coma. Large amounts of insulin (total, 230 units within twelve hours) failed to bring the blood sugar below 0.40 per cent, and death occurred the day following entry. Necropsy showed atrophy of the pancreas, with "hyalo-fibrinoid changes in the islands." The bone marrow was gray-red in color, containing a moderate number of megaloblasts, numerous normoblasts and eosinophils.

Adams describes a second woman, aged fifty-six years, who gave a history of mild diabetes. Onset of sore mouth and tongue occurred eight years later; paresthesias two months prior to entry. Examination revealed an atrophic tongue, diminished vibratory sense in the lower extremities. Stomach contents contained no free HCl. Fasting blood sugar was 0.23 per cent. The color index was 1 or slightly under; there was moderate variation in size and shape of the erythrocytes in the stained film.

The same author refers to a third case in the series of 1000 primary anemias and 2000 diabetics, which he reviewed. This patient, a diabetic of long standing, developed primary pernicious anemia while under the care of another physician. Further data were not obtained.

In the above reports, the criteria for the diagnosis of primary pernicious anemia vary. The reviewer consequently cannot be certain in the cases which failed to come to autopsy that the pernicious anemia was the clinical entity, or was possibly a severe

CHRONOLOGICAL OUTLINE OF CASE OF C. L. TO SHOW PROGRESS OF DIABETES AND PERNICIOUS ANEMIA.

Date.	Symptoms.	Hemoglobin per cent.	Erythrocytes in millions.	Urine sugar.	Fasting blood sugar, gm. in 100 cc.	Treatment.	Remarks.
May 5, 1925	Weakness, giddiness polydipsia, polyphagia, polyuria	"Heavily loaded"	0.228	Diet, P. 50, F. 200, C. 75, insulin 30 U.	Appeared a typical diabetic. Anemia not suspected.
Mar. 6, 1926	Tingling, numbness in hands and feet	42	1.50	0	"Normal"	5 transfusions total 2500 cc.	No evidence of diabetes. Normoblasts, aniso- and poikilocytosis in blood film.
May 7, 1926	Weakness, vomiting, fleeting pains in arms and legs	88	4.50	0	"Normal"	Dilute HCl 1 cc. t. i. d.	Remission following transfusions. Entered University Hospital. Gastric anacidity. Blood film that of pernicious anemia. No blood in stools. No evidence of diabetes.
Oct. 15, 1926	No change	30	1.25	0	..	Minot-Murphy diet started (liver 50 grams) Liver 200 grams dilute HCl 3 cc. t. i. d.	Indirect van den Bergh, 1 unit.
Oct. 28, 1926	Feels stronger, no gastric disturbance	42	1.75	0	Leukocytes increased to normal figure. Trace albumin; several hyalin and granular casts.
Nov. 5, 1926	Pain in legs gone	64	2.90	..	0	No excretion of neutral red by stomach glands.
Nov. 11, 1926	No change	70	3.25	0	Discharged.
Nov. 18, 1926	No change	70	3.50	Caught cold at home, January 10, 1927.
Nov. 27, 1926	No symptoms	83	4.80	Carious tooth extracted	Readmitted. Dehydrated. On verge of diabetic coma.
Jan. 3, 1927	No symptoms	93	4.40	+	0.375	Intravenous glucose and insulin	Albumin and casts.
Feb. 8, 1927	Polyuria, vomiting, pain in back	120	6.30	ketonuria	0.375	Occasionally mild insulin reaction.
Feb. 10, 1927	70	4.40	+++	0.250	Diet, P. 60, F. 90, C. 80, insulin 50 U.	Diarrhea. Trace occult blood in stools. Gastric anacidity after histamin subcutaneously.
Feb. 17, 1927	Much stronger	76	4.95	0	0.082	Diet, P. 60, F. 160, C. 100, insulin 10 U.	No insulin. No liver. Discharged.
Mar. 1, 1927	87	4.10	0	0.102	Diet, P. 60, F. 160, C. 100, (approx.) Dil. HCl 2 cc. t. i. d.	Takes liver once or twice a week.
Mar. 18, 1927	71	3.90	0	..	Insulin 20 units daily	
Nov. 18, 1927	80	4.00	Occasionally present	..		
April, 1928	Occasional weak and dizzy spells. Numbness continues				

secondary process due to prolonged mild bleeding. We have two completed cases, however, and must presume that the other four anemias also were of the primary type.

Case Report. C. L., white, a coal miner, aged forty-one years, was admitted to the hospital of the University of Pennsylvania, on the service of Dr. Alfred Stengel, October 14, 1926, complaining of weakness and vomiting. He had been in normal health until March, 1925, when he began to notice weakness and giddiness, excessive thirst and hunger. Two months later he was admitted to a hospital near his home, which hospital has kindly furnished a brief summary of the patient's record. Diabetes mellitus was there diagnosed upon finding glycosuria and a blood sugar of 0.228 per cent. Blood count was not made. Sugar and symptoms disappeared on a diet of 2300 calories, with daily insulin of 30 units. The patient was discharged, to return to the hospital ten months later with a history of having remained sugar-free, in spite of very irregular diet and no insulin. He had been at work in the interval.

On the second admission, blood sugar was normal, and on maintenance diet the patient showed no sugar at any time. He had developed, in the interval, however, a severe anemia, and on entry showed a hemoglobin of 42 per cent, 1.5 million erythrocytes and 4500 leukocytes. The stained film showed aniso- and poikilocytosis and normoblasts. Five transfusions of 500 cc. each served to allow his discharge after six weeks, with 4.5 million erythrocytes and 88 per cent hemoglobin. Pernicious anemia was the only diagnosis made on this second admission.

Following the second discharge the patient was able to work for only two weeks because of recurrence of weakness, dyspnea, paresthesias, sore mouth and tongue. He was referred to the hospital of the University of Pennsylvania from his home, when it was discovered that the anemia had returned to an alarming degree.

Physical examination on entry October 15, 1926, showed good development and nutrition, very pale skin and mucous membranes, with a yellowish cast. The tongue was moist, a little smooth. Heart and lungs were negative. The spleen tip was palpable. Vessel walls were soft. Reflexes were normal; vibratory sense was found diminished in the lower extremities. Rectal examination was negative. Blood pressure was 105 systolic, 60 diastolic. Temperature, pulse and respiratory rate were normal. Tentative diagnosis was primary pernicious anemia.

The significant laboratory findings are charted in the accompanying table.

There was no evidence of bleeding in the gastrointestinal tract at this time; the fluoroscopic study in a gastrointestinal Roentgen ray series, otherwise negative, gave suspicion of slight pyloric irregularity. There was no indication of kidney damage.

On a Minot-Murphy regime, in which the amount of liver was quickly raised to 200 gm. daily, the patient improved remarkably, and was discharged six weeks after entry, with a blood picture which was normal except for variation in size of the erythrocytes.

The patient kept to the liver diet at home, and was well for a month when he appeared for follow-up and further Roentgen ray study of his stomach. The blood picture remained as at time of discharge. Again, Roentgen ray was barely suggestive of hypertrophied mucosa in the pyloric region.

Shortly after this visit the patient caught cold, and in a few days began to notice polydipsia, polyuria and incontinence of urine. He lost weight and appetite, became nauseated and drowsy; and was readmitted in that

state February 8, 1927, vomiting frequently. His condition at this time was that of severe diabetic acidosis. Blood sugar was 0.375 per cent; plasma CO_2 , 20 vol. per cent; and all the measures of routine acidosis care were needed to bring about recovery. When the sugar tolerance began to rise, it came back rapidly, and the patient experienced several mild hypoglycemic reactions before insulin was finally omitted entirely four weeks after entry, with a maintenance diet. The initial polycythemia shown on the chart disappeared as the dehydration was relieved; and the blood count was noted further to fall slowly. No liver was given in the diabetic trays of this period.

On this, the patient's second admission, vibratory sense was absent in the lower extremities, diminished over pelvis and spine, but present in the upper extremities and shoulder girdle. The signs of an acute nephritis, also present on admission, cleared slowly. Two readings of blood urea nitrogen were normal, and the elimination of 'phthalein by the intravenous method was 55 per cent in two hours.

A third analysis of stomach contents showed total absence of free HCl and ferments, after the ingestion of 100 cc. of 5 per cent alcohol and also after the injection of 1 cc. of 1:1000 histamin subcutaneously. Stomach roentgenograms again suggesting hypertrophy of the pyloric mucous membrane, and small amounts of occult blood appearing in the stools, exploration was thought advisable by certain members of the staff who had in mind the condition simulating pernicious anemia caused by prolonged oozing from a gastrointestinal lesion. The operation was explained to the patient who decided against it. He was then discharged to the care of his local physician, slightly anemic, but symptomless, with advice to renew the liver diet on reaching home.

The patient reported by letter, after eight months, that his blood count showed 4 million erythrocytes, hemoglobin 80 per cent. He feels well most of the time, except for occasional week-long spells of weakness and dizziness. Numbness of legs and feet continues. He takes liver once or twice a week, has shown sugar in the urine from time to time and when last heard of, in April, 1928, a year after discharge, was taking 20 units of insulin daily.

Summary. 1. Six instances of diabetes associated with pernicious anemia have been found reported in the medical literature.

2. The anemia was considered the first condition to develop in 3 cases; diabetes first in 2; and in the remaining instance, both conditions were found simultaneously.

3. Necropsy findings in 2 instances confirmed the diagnoses. In the other 4, the blood picture and course of the disease were taken as evidence of pernicious anemia.

4. A case is here reported in detail, in which the diabetes evidently antedated the anemia by several months, and was not in evidence during the height of the anemia as observed in the hospital. It reappeared however, several weeks after the patient had entered a complete remission on a Minot-Murphy liver diet.

5. The diabetes, furthermore, is here mild, with two acute exacerbations, not associated with the anemic state.

6. Concerning the diagnosis of pernicious anemia, the one disturbing factor, in a clinical picture otherwise complete, is roentgenographic evidence of possible hypertrophied pyloric mucosa, which

may be bleeding slowly, although occult blood was found on only two of the many stool examinations.

7. Finally, the present study indicates, at least so far as reported clinical findings are concerned, that there exists no consistent relationship between primary pernicious anemia and diabetes. The cases so far discovered should be considered as coincidences.

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THE INTRACUTANEOUS SALT-SOLUTION TEST IN THYROTOXICOSIS.

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IN 1923, McClure and Aldrich¹ first described the intracutaneous salt-solution test. They injected 0.2 cc. of 0.85 per cent aqueous solution of sodium chlorid intradermally (aseptically) into the flexor surface of the forearm, inner surface of the calf, or the lateral side of the anterior surface of the leg. A duplicate injection was made 2 cm. away. The end point of the disappearance of the elevation was determined by palpation unassisted by inspection. The raised area produced persisted for sixty minutes or more in normal cases. They found that in cases of edema there was a decided reduction of the disappearance time, the latter being roughly in inverse ratio to the degree of edema at the area of injection. In a subsequent communication,² the same authors reported application of the test to 16 children with generalized edema and urinary findings of albumin, casts, and red blood cells, but unassociated with nitrogen retention or evidence of cardiovascular disease. They were able to prognose with considerable accuracy the appearance and disappearance of edema, and felt that the test showed these changes earlier than any other method. It also seemed to substantiate the theory that the tissues in this type of

case are active in the development of the edema. Baker³ studied the test in 70 cases of scarlet fever and 30 cases of diphtheria (two-thirds of whom were children) and found reduction of the disappearance time, the reduction being parallel to the severity of the intoxication.

A group of children with lobar pneumonia was tested by Harrison,⁴ who found a considerable shortening of the disappearance time, with a slow return to normal after the crisis, suggesting a more persistent intoxication of the tissues than is usually considered. Lash⁵ applied the test to patients with normal and toxemic pregnancies. In the latter condition there was a definitely decreased disappearance time more marked in those patients with convulsions. The degree of decrease in the disappearance time varied directly with the degree of severity of the toxemia, increasing with the general clinical improvement. Lash suggested that the test might prove of value in determining the oncoming of a toxemia earlier than by any other available method. Cohen⁶ observed that intradermally-injected salt solution disappeared more rapidly from areas with deficient circulation than from those areas in which the circulation was normal, in a manner comparable to the difference observed in different parts of the body in cardiac disease. Cohen believes that the test affords a simple method of determining the level of adequate tissue oxygenation. Stern and Cohen⁷ state that in all instances in which clinical circulatory deficiency exists, the disappearance time is diminished; in the area just above the seat of gangrene (existing or threatened) it is frequently as low as five minutes. In 4 myxedematous patients, Thompson⁸ noted the disappearance time as being more consistently prolonged before or in the interval of thyroid omission than during the period of administration. (In all other types of edema the disappearance time has been found to be markedly diminished.) In a group of children with rheumatic heart disease and allied conditions, Olmsted⁹ found that the disappearing time was normal in well-compensated nontoxic cases and in decompensation with edema shortening of the disappearance time was limited to edematous and præedematous regions and was noted earliest in the dependent portions of the body. In these cases, the decrease in disappearance time did not precede other clinical signs of impending decompensation with sufficient constancy to make the test of much value in predicting a break in compensation. A reduced disappearance time was frequently found postoperatively by Appel and Brill,¹⁰ who suggested this test as a method for determining the need of the tissues for water. Kunde¹¹ extended the study of the test to a series of adult patients with different forms of nephritis, typhoid fever, toxemias of pregnancy and other conditions, and attempted to correlate the observations with regard to the time necessary for the disappearance of the wheal with observations made with the elastometer and those made on urine and blood. By means of this test Bradford¹² found a definitely increased

avidity of the tissues for water in serum sickness' Pla¹³ noted a decreased disappearance time in intoxication with vomiting and diarrhea, catharsis, or any kind of ascites. The work of Feldman and Reifsneider¹⁴ confirms the fundamental fact of the rapid disappearance of the elevation made by intradermally injected saline solution in nephritic edemas. Amitrano¹⁵ observed that in newborn infants the cutaneous absorption of sodium-chlorid solution was invariably hastened. Recently, Feldman¹⁶ found a decreased disappearance time in pulmonary tuberculosis.

The mechanism of the test is not entirely clear. Guggenheimer and Hirsch¹⁷ offer a mechanical hypothesis to explain the rapid absorption of salt solution by edematous tissues. Cohen¹⁸ and his colleagues believe that the mechanism of reaction is that of an increased affinity of the tissues for water, based largely on the work of Martin Fischer¹⁹ who postulated that the normal turgor of a tissue depends on the physical state of its colloids and that edema results whenever the water-holding power of its colloids is increased and when a supply of free water is available. It may be that a possible difference between capillary pressure and the osmotic pressure of the blood can account for the phenomenon.

The present study comprised a series of 42 cases of thyrotoxicosis. There were 36 women and 6 men. The youngest was fourteen, the oldest sixty-nine years of age. The duration of the illness varied from one month to twenty-two years. There were 35 cases of the so-called "hyperplastic goiter" type (exophthalmic goiter) and 7 cases of "toxic adenoma." Two of the former group represented recurrences (having been previously operated upon elsewhere). The test was performed according to the original technique of McClure and Aldrich, the wheals being made on the flexor surface of the right forearm below the cubital fossa, and the end point determined by palpation. The tests were made at varying intervals before and after operation, being checked up in each case by determinations of the basal metabolic rate. A control series of injections was made in a group of nontoxic goiter patients. Care was taken to exclude from this study any case exhibiting gross cardiac or renal damage, or any acute infectious process.

It was extremely interesting to note that in every instance there was a definite decrease in the disappearance time of the intradermally injected saline solution before operation; (normally sixty minutes or more are required for the wheal made by injected salt solution to disappear). After operation, with the return to normal of the basal metabolic rate and the patient's general condition, the disappearance time also returned to normal. While no exact mathematical ratio can be expressed, it may be stated that in general the more toxic the patient the more rapid the disappearance time of the wheal, and that the latter parallels the basal metabolic rate as a measure of the severity of the toxemia.

The complete protocol is presented in the accompanying table.

TABLE SHOWING AGE OF PATIENTS, DURATION OF ILLNESS, PREOPERATIVE AND POSTOPERATIVE DISAPPEARANCE TIME OF SALT-SOLUTION WHEELS WITH CORRESPONDING BASAL METABOLIC RATE DETERMINATIONS.

Case and No.	Age.	Duration.	Preoperative basal metabolic rate, plus.	Preoperative disappearance time, minutes.	Postoperative basal metabolic rate.	Postoperative disappearance time, minutes.	Type of goiter.
1. A. W.	38	2 years	56	15	-10	72	Hyperplastic.
2. S. T.	39	5 months	37	40	-7	65	Hyperplastic.
3. M. L.	55	4 months	46	25	+15	55	Hyperplastic.
4. J. R.	28	2 years	32	48	-3	70	Hyperplastic.
5. L. L.	20	1 year	33	37	0	60	Hyperplastic.
6. S. M.	49	9 months	30	32	-12	65	Hyperplastic.
7. H. S.	14	1 year	50	30	-10	65	Hyperplastic.
8. L. L.	50	6 weeks	40	40	-11	71	Hyperplastic.
9. R. K.	41	3 years	30	33	-6	59	Hyperplastic recurrent.
10. A. S.	48	18 months	38	32	0	70	Adenoma.
11. H. S.	36	9 months	44	45	-11	61	Hyperplastic.
12. M. G.	60	2 years	43	35	0	58	Adenoma.
13. B. S.	52	6 months	57	27	+6	60	Hyperplastic.
14. E. F.	24	6 months	55	28	+3	59	Hyperplastic.
15. R. M.	31	7 months	55	22	+8	56	Hyperplastic.
16. M. N.	15	4 months	27	45	-10	62	Hyperplastic.
17. S. G.	30	4 months	36	18	-13	69	Hyperplastic.
18. M. S.	48	4 months	60	29	+2	61	Adenoma.
19. A. L.	21	1 year	19	50	-10	63	Adenoma.
20. G. M.	45	4 years	31	34	-5	68	Hyperplastic.
21. R. H.	30	3 months	71	20	-10	72	Hyperplastic.
22. T. S.	38	1 month	85	17	+10	59	Hyperplastic.
23. G. R.	32	6 months	22	44	+3	65	Hyperplastic.
24. B. R.	34	4 years	48.5	30	-9	68	Hyperplastic.
25. C. L.	19	3 months	51	26	-3.5	64	Hyperplastic.
26. V. K.	33	2 months	17	48	-4	59	Hyperplastic.
27. C. S.	32	6 months	28	45	-14	66	Hyperplastic.
28. D. G.	23	4 months	51	19	-8.8	67	Hyperplastic.
29. G. S.	46	3 months	19	50	-9	60	Adenoma.
30. E. G.	40	1 year	49	27	+8.5	60	Hyperplastic (recurrent).
31. I. P.	28	Many years	36	40	-23	78	Adenoma.
32. E. L.	34	6 months	17	55	-21	85	Adenoma.
33. A. P.	29	2 months	52	45	+3	65	Hyperplastic.
34. A. B.	32	18 months	35	30	-4	66	Hyperplastic recurrent.
35. R. S.	69	6 months	66	36	+1.3	59	Hyperplastic.
36. F. C.	22	2 months	37	40	+6	61	Hyperplastic.
37. V. Z.	28	7 months	52	30	+1.6	66	Hyperplastic.
38. C. D.	29	4 years	33	27	+3.3	62	Hyperplastic.
39. J. S.	44	22 years	60	19	+4.4	66	Hyperplastic.
40. A. J.	27	2 months	52	25	+7	63	Hyperplastic.
41. R. C.	27	2 months	51	35	-26	70	Hyperplastic.
42. M. H.	31	2 months	33	37	+2	64	Hyperplastic.

Summary. 1. The intracutaneous salt solution test was studied in 42 cases of thyrotoxicosis, before and after operation.

2. There was a definite decrease in the disappearance time of the wheal preoperatively. After operation, with the return to normal of the basal metabolic rate and the patient's general condition, the disappearance time also became normal.

3. In a general way, the greater the toxemia, the less time was required for the wheal to disappear.

4. The disappearance time of the intradermally injected saline solution paralleled the basal metabolic rate as an index of the severity of the thyrotoxicosis.

5. The literature pertaining to this test is reviewed.

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A SIMPLE EXERCISE TOLERANCE TEST FOR CIRCULATORY EFFICIENCY WITH STANDARD TABLES FOR NORMAL INDIVIDUALS.

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For many years a variety of exercise tests have been utilized for the investigation of circulatory efficiency, including stair climbing, hopping, dumb-bell swinging, ergometer trials, and so forth. Of

these, no one method has proved entirely satisfactory, as shown by the diversity of tests suggested. Records of blood pressure, systolic and diastolic, and of pulse rate have been used most frequently as the criteria of the circulatory reactions.

As early as 1901, Mendelsohn using an ergostat, recorded the pulse changes following exercise, and Graupner, in 1906, plotted curves of blood-pressure variations after periods of muscular work.

Selig was the first to use the stair-climbing test. No quantitative measurements in foot-pounds were made, nor was the rate of running considered. Selig noted that an advantage of the stair-climbing test was the complete freedom of the thoracic movements; in other words, that there was no interference with the normal functions of the body, an advantage absent in some of the other tests.

Kahn introduced a test consisting of hopping 100 times on one foot and roughly estimated that this work averaged 3750 foot pounds.

The popularization of the dumb-bell exercise test was the work of Barringer. Dumb-bells of from 3 to 25 pounds each were used. He omitted the diastolic blood-pressure readings, as he found them of little value. He demonstrated that the amount of work necessary to produce a delayed rise in systolic blood pressure was the same whatever group of muscles was employed. Work performed with the arm and back muscles was found to give the same results as work with the thighs and legs.

Cotton, Rapport and Lewis considered not only the total amount of work done, but also the rate of work.

Rapport utilized stairs of 45 and of 90 steps respectively, each step 9 inches high, which were mounted with varying rapidity. No attempt was made in his experiments to calculate the exact amount of work performed.

Recently, Dr. May Wilson has made use of 25 and of 60 steps in an exercise tolerance test. The total heights of the steps were 15 and 30 feet respectively, and were climbed in from twenty to forty seconds. Quantitative measurements were made, but age, sex and height were not considered. Dr. Wilson also found that circulatory reactions following the stair-case and the rope-jumping tests were similar to those obtained with the dumb-bell exercise.

On a plan somewhat similar to that described in this paper, Felberbaum and Finesilver have used a test consisting of ascents of two steps, each 6 inches high. The duration of the exercise was not, however, kept constant; nor apparently were age, sex, height or weight considered; moreover, a 6-inch step seems to us too small.

In 1926, Wolffe described an ergometer which measured the work performed by the arms in rotating a disc against friction. His method may be taken as an illustration of the type of test utilized for work by upper or by lower extremities. The stationary bicycle is an example of the latter. The muscular movements involved in this type of exercise are, however, not sufficiently common for clinical use, and the psychic element may play a considerable rôle.

None of these tests, therefore, seemed exactly suitable for the purposes of the present investigation, which originated in an attempt to study variations in exercise tolerance in certain pathologic conditions. A test was desired which would: (1) permit accurate measurement of the work performed; (2) involve only an ordinary everyday muscular activity; (3) be simple enough for use in a hospital clinic or in a physician's office. Most of the tests hitherto used are applicable only to certain types of subject, so that statistics obtained with one test cannot be compared with those gained with another variety of exercise on a different type of individual. Before conclusions can be drawn from the investigation of pathologic conditions standards must be established with the same test on the normal individual.

The physician desires a test to help in diagnosing cardiac insufficiency, and to indicate improvement or the reverse in circulatory conditions. A quantitative test, applicable to all, might throw much light on the course of certain forms of heart disease.

The test we finally adopted consisted of ascending and descending two steps a variable number of times in a given period of time. Even in these days of elevators, stair climbing is work occasionally performed by everyone, so that an ascent of two steps arouses no apprehension or excitement on the part of the subject, and psychic disturbance is at a minimum. This is extremely important, since mental reactions may undoubtedly cause acceleration of the pulse rate and a rise of blood pressure, thus influencing the very factors which are to be utilized for studying the circulatory response to exercise.

This test has the further advantage of being absolutely standardizable, and of allowing exact measurement of work for patients of any weight. Dumb-bell exercises, hopping, skipping, and the like are all capable of varying interpretation according to the intelligence, vigor and goodwill of the individual patient. With stair climbing the only variation possible is in the rate of ascent and descent, a variation which is easily regulated, and which in any case appears in the final calculation of the foot-pounds of work performed.

Method of Observation. For convenience in performing the test, we devised a simple two-step contrivance made out of $\frac{3}{4}$ inch pine wood, and consisting of two steps up on one side and two down on the other, as illustrated in Fig. 1. Each step is exactly 9 inches high (and about 22 inches wide). This apparatus does not look foreboding, and moreover can be conveniently kept in the office and utilized as a seat or shelf, or placed out of the way under a table.

Blood-pressure readings were made by the auscultatory method, and heart rate was recorded by counting the radial pulsations. Both diastolic and systolic blood pressure were noted in every case, but for the purposes of this paper only the *systolic* was considered.

These observations were made first with the subject at rest in the sitting position (Fig. 2), care being taken that sufficient time should

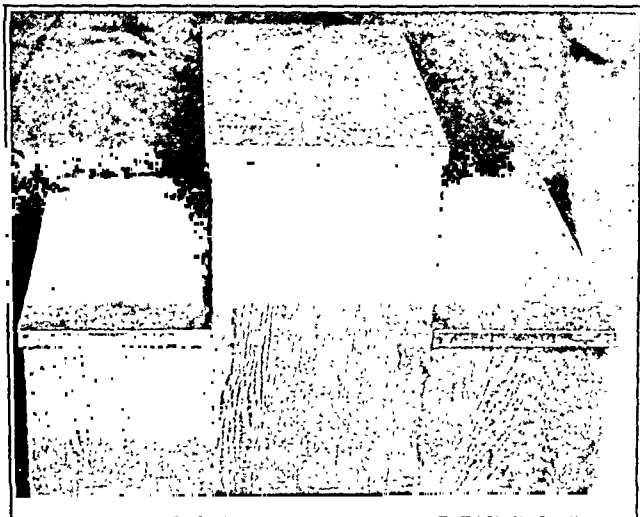


FIG. 1.—Steps for exercise tolerance test. Each step 9 inches high.



FIG. 2.—Obtaining resting blood pressure and pulse.

elapse for the circulatory conditions to reach a true resting level. In our earlier experiments, in order to eliminate mental factors as far as possible, we made a rule of always discarding the first test, and accepting only later ones. It was found, however, that a second test almost invariably gave the same results, if the first were made with the precautions suggested. This, we believe, indicates that the test produces a negligible degree of excitement.

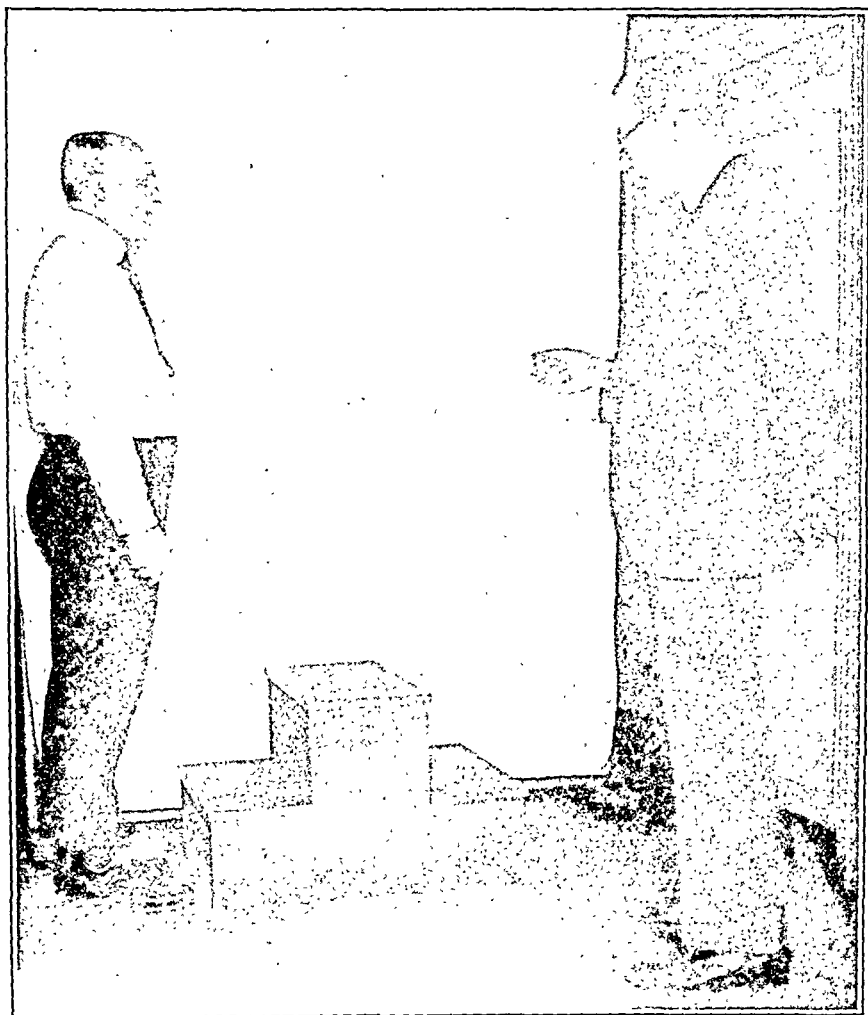


FIG. 3.—Ready to start test.

The patient then ascended and descended the steps for a minute and a half (Figs. 3 to 12), resumed his seat, and the exact time was noted when blood pressure and pulse rate returned to their pre-exercise (resting) level. For a satisfactory performance of the test, this resting level must be reached within two minutes of the termination of the exercise. The amount of work done may, of course, be varied according to the number of ascents made in the allotted time. With each subject, therefore, we gradually increased the number of

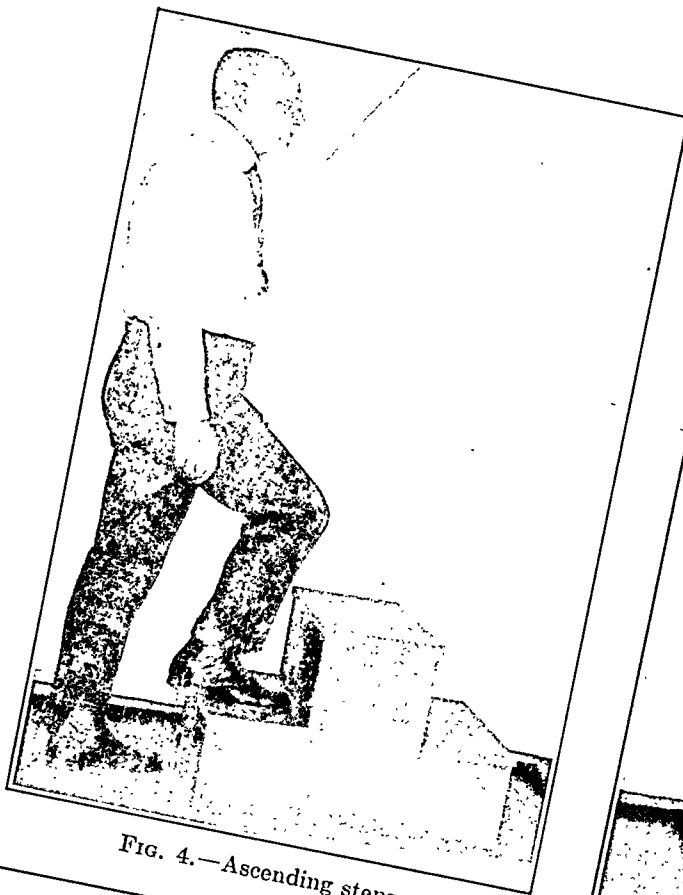


FIG. 4.—Ascending steps

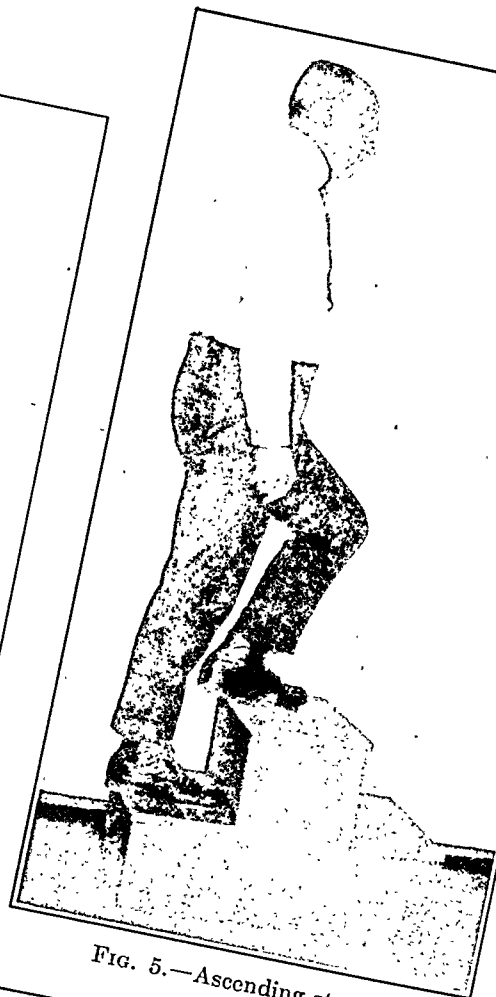


FIG. 5.—Ascending steps.



FIG. 6.—Descending steps.



FIG. 7.—Turning to left (that is, toward the wall).

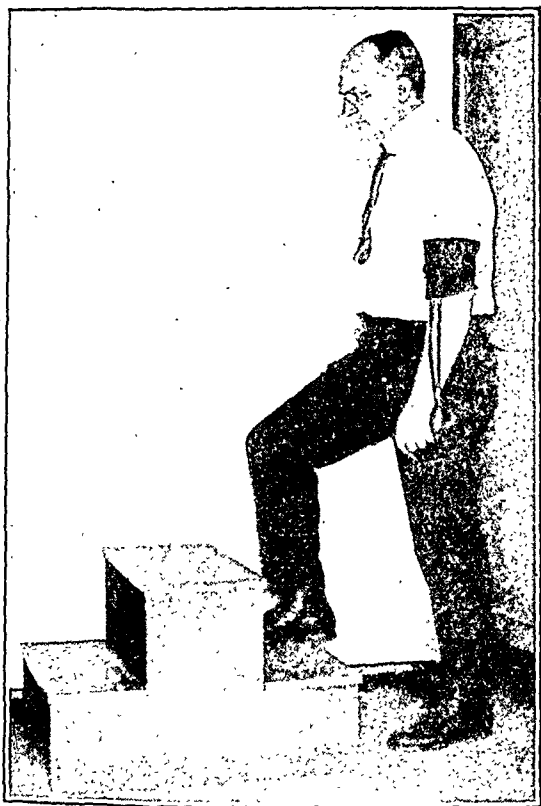


FIG. 8.—Retracing course.



FIG. 9.—Retracing course.

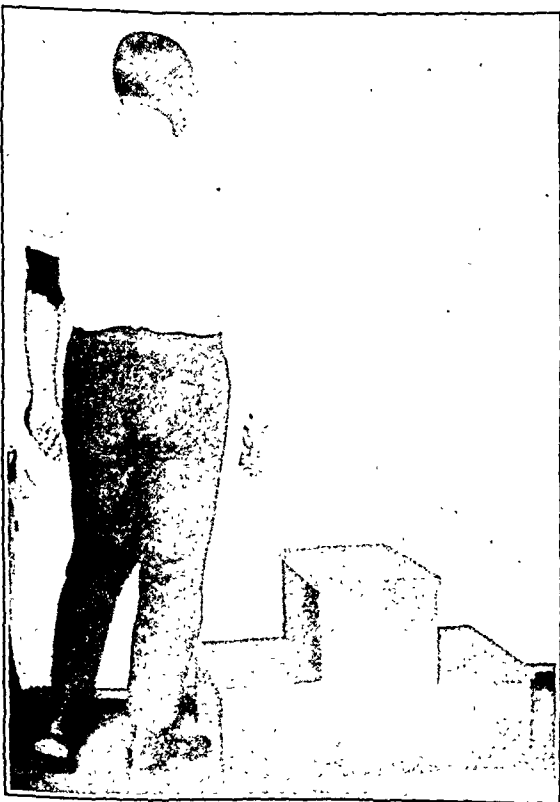


FIG. 10.—Turning to right (that is, toward same wall).

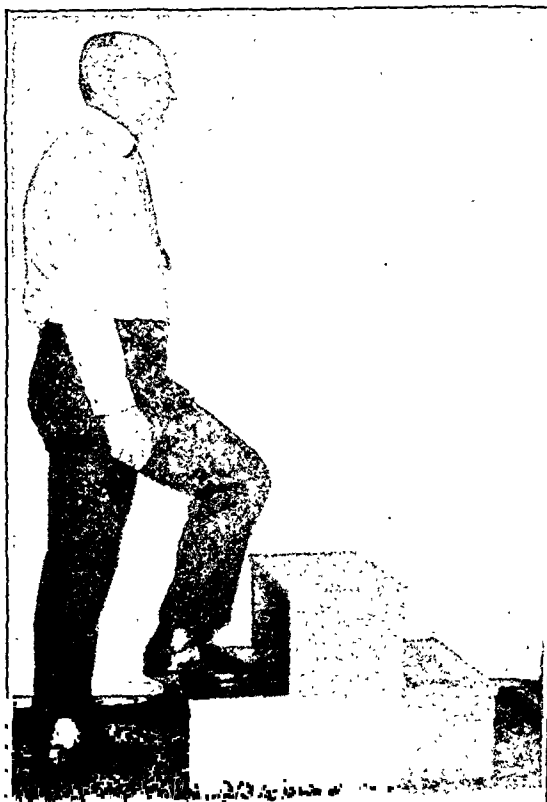


FIG. 11.—Commencing third ascent.

ascents until the maximum number was reached which could be accomplished without delaying the return to resting circulatory conditions beyond the prescribed two minutes. The choice of one and a half minutes as the duration of the period of exercise was made after much experimentation, which showed that a short period of more violent exercise was not so satisfactory.

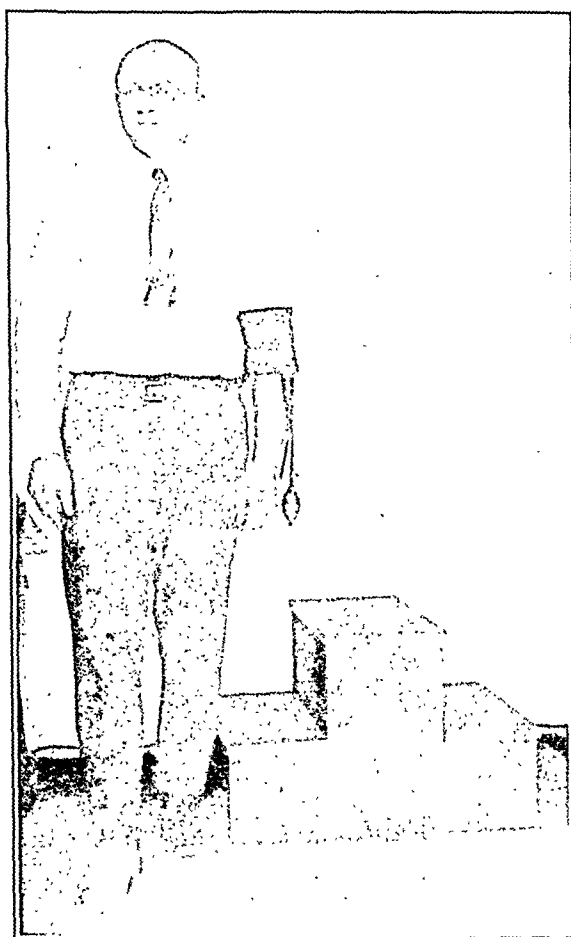


FIG. 12.—Returning to desk at end of minute and a half of exercise.

The calculation of the amount of work done is simple. The individual raises himself to a height of 9 by 2 inches, or $1\frac{1}{2}$ feet, each time he mounts the steps. The work in foot-pounds at each ascent is, therefore, the product of his weight in pounds by $1\frac{1}{2}$, so that the total work is this product multiplied by the number of ascents. On the descent, there is no actual lifting of the weight against gravity. Since any work done in descending will be comparatively small in amount, and exactly proportional to the work done on the ascent, for the sake of simplicity this is omitted in the calculation. Thus, a man of 150 pounds, mounting the steps 20 times will do 150 by 20 by

$1\frac{1}{2}$, or 4500 foot-pounds of work. This is done in one and a half minutes, so that the work done in one minute will be

$$\frac{150 \times 20 \times 1\frac{1}{2}}{1\frac{1}{2}}$$

or 3000 foot-pounds per minute. Obviously, the figures $1\frac{1}{2}$ cancel each other, so that the rate of work per minute may be obtained merely by multiplying the patient's weight by the number of ascents. This is an additional advantage of fixing the period of exercise at the exact space of time of one and a half minutes.

In this way, we determined the maximum number of foot-pounds of work which could be done by normal individuals per minute, with a return to resting circulatory conditions in two minutes. In order to determine standards for different types of persons, we estimated by this method the exercise tolerance of 115 normal subjects, 59 males and 56 females, of varying weights and heights within normal limits, and of ages ranging from ten to seventy-four years. The individuals tested were chosen from many different types of occupation, but extremes such as laborers or athletes, the very obese or the abnormally thin, were excluded. Each of the cases presented was carefully investigated, and a thorough physical examination made, and in more than one-half of the subjects teleorentgenograms and electrocardiograms were taken. Any case presenting the least abnormality was excluded from the series.

Discussion of Results. From the figures of exercise tolerance thus obtained in foot-pounds of work, it appeared clear that the factors of age, sex, weight and height were of extreme importance, and must be carefully considered in any attempt to establish normal standards of work. Graphs were, therefore, plotted with foot-pounds of work as ordinates, and age (Fig. 13), weight (Fig. 14) and height (Fig. 15), respectively, as abscissæ. These curves must be considered together since the three variables of age, weight and height are so closely connected, but interesting features may be brought out by a preliminary study of each curve separately.

Considering first the graphs showing the relation between exercise tolerance and age (Fig. 13), we find that the curve for males, as would be expected, shows the steepest rise between ten and twenty years of age. A more gradual rise occurs to a maximum at about twenty-seven years, when 3795 foot-pounds of work per minute is reached. Thereafter a gradual decline occurs, and at seventy-four years the work done is only 2250 foot-pounds. Females reach a maximum of 2950 foot-pounds at about twenty-four years of age, the rise being most rapid between ten and thirteen years. It is important to note that before puberty girls are better than boys, whereas after thirteen years of age, boys take and men keep, the lead. This conclusion is also borne out by the curves for weight and height (Figs. 14 and 15).

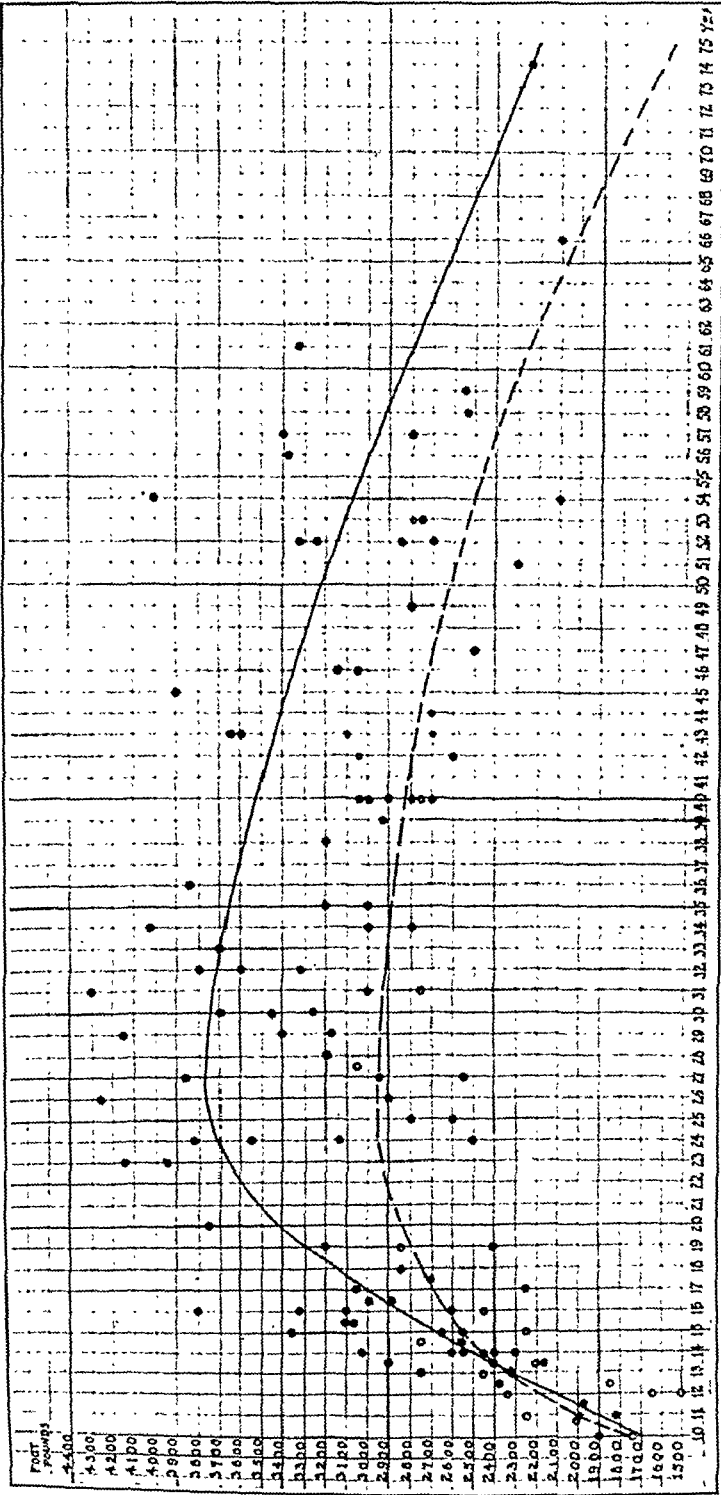


Fig. 13.—Curves of foot-pounds and ages. Full dots and line for males, small circles and broken line for females.

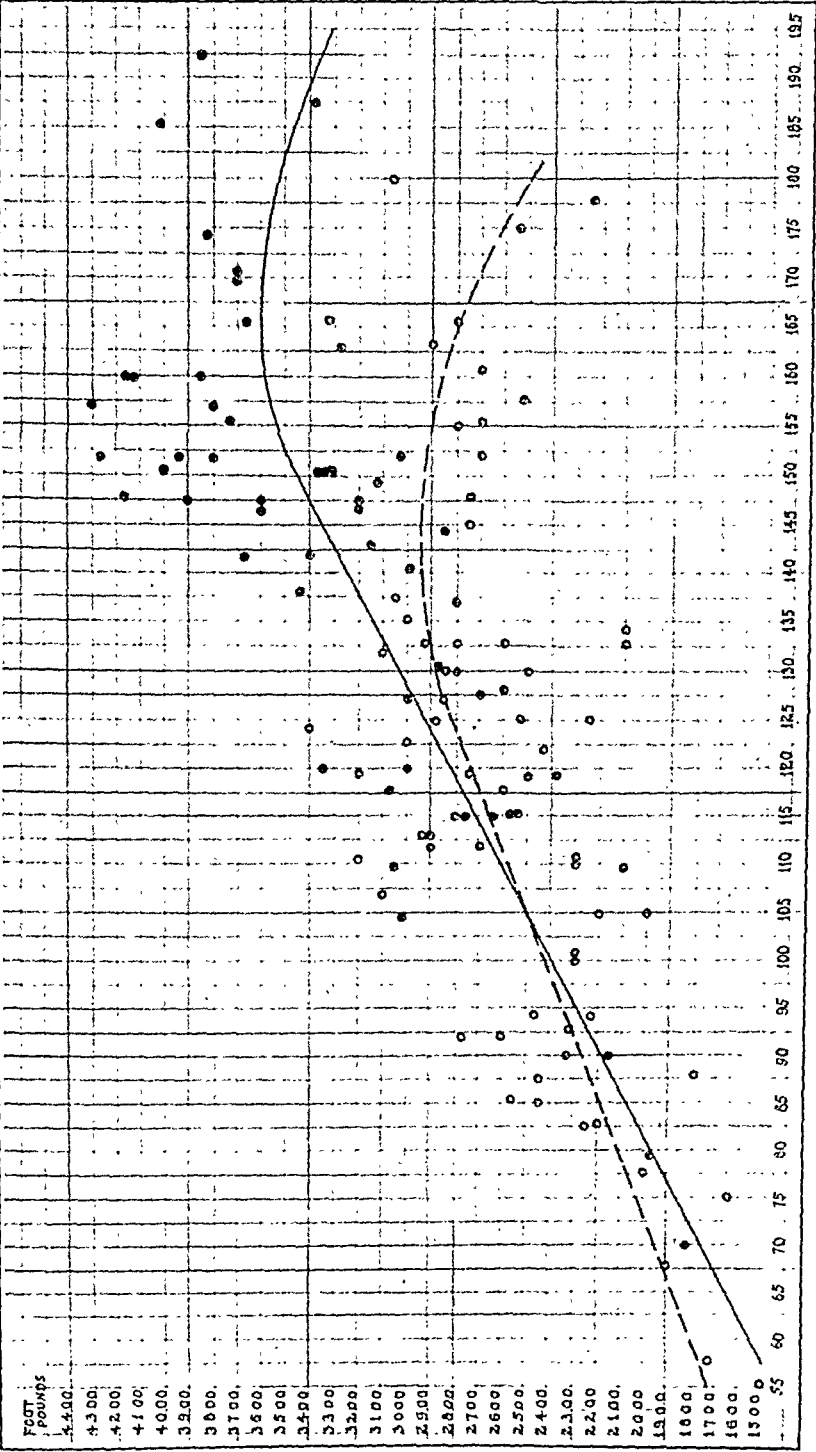


Fig. 14.—Curves of foot-pounds and weight. Full line for males, broken line for females.

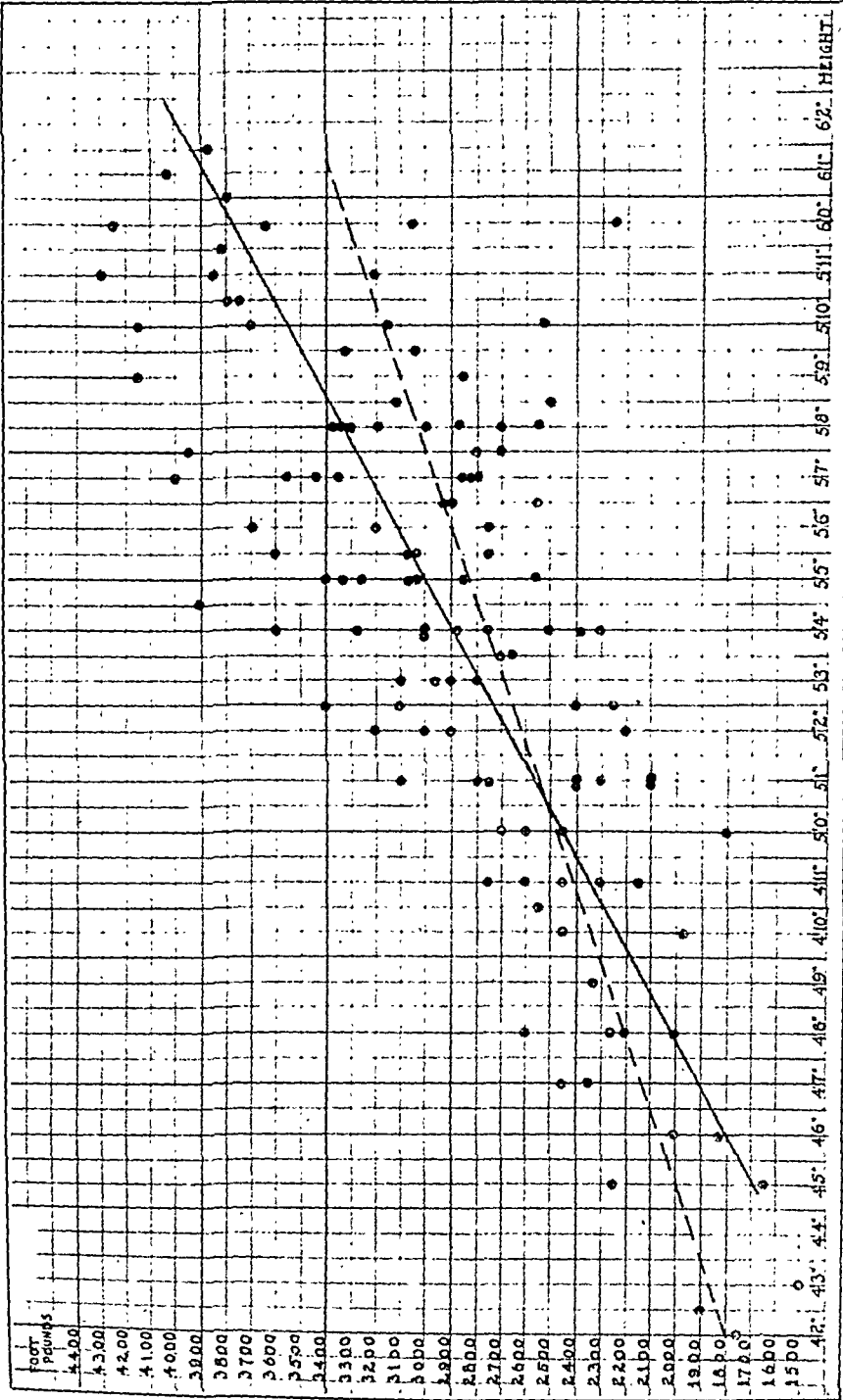


FIG. 15.—Curves of foot-pounds and height. Full line for males, broken line for females.

The relation between work and weight is expressed for the most part by a straight line, work capacity rising in direct proportion to increasing weight. However, after 160 to 165 pounds in men, and 135 to 145 pounds in women, there is a fall in the curve, the subjects at this weight being apparently the most efficient.

A straight line also expresses the relationship between work and height. Here the continuous rise is accounted for by the fact that taller individuals have a mechanical advantage over smaller ones in climbing a step. Males again show an advantage over females, except at the low statures of childhood, when girls do better than boys.

The steep rises in the "age" curves between ten and twenty years are clearly influenced by the great increments of weight and height during these early years. These same factors also account partly for the generally better performance of men compared with women, but not entirely, since a man always shows a higher exercise tolerance than a woman even of exactly the same weight, height and age. This is, of course, due to a greater proportion of skeletal muscle tissue per unit of body weight.

It is interesting to note that at the optimum age for this test, men have an average tolerance of about 3800, and women of about 3000 foot-pounds. That is to say, men have a work capacity of approximately $\frac{1}{8}$ horsepower, and women of about $\frac{1}{11}$, values which agree with results obtained by engineers.

Use of the Standard Tables. In order to make these data readily available as a standard test, it was essential to present them in such a form that the normal exercise tolerance for any combination of height, weight, age and sex could be obtained. The statistical treatment necessary to do this is explained in the appendix.

As the result of such treatment, the series of figures given in Tables I and II were obtained. These two tables—one for males, the other for females—give the number of foot-pounds of work arranged with regard to age and weight. Each horizontal line gives the foot-pounds of work corresponding to a particular weight at different ages, and each vertical column presents the foot-pounds corresponding to different weights at a particular age. A value can, therefore, be found for a person of either sex of any age and of any weight. To obtain variation for height a simple correction is made for individuals above and below 5 feet 4 inches. For females of all ages 25 foot-pounds are added for every inch of height above 5 feet 4 inches, and subtracted for every inch below. For men under twenty-one years, 50 foot-pounds are added or subtracted in exactly the same way. For men over twenty-one years, no correction should be made.

Since the table does not give values for every year of age, but often only for alternate years, figures for the missing ages are obtained by taking values intermediate between the figures for the years above and below.

TABLE I.—MALES. TWO-STEP EXERCISE TOLERANCE TEST.

CORRECTION FOR HEIGHT. ADD 50 FOOT-POUNDS FOR EVERY INCH ABOVE 5 FEET 4 INCHES AND SUBTRACT FOR EVERY INCH BELOW 5 FEET 4 INCHES. NO CORRECTION FOR MEN OVER TWENTY-ONE YEARS OF AGE.

Age in Years

Weight	10	11	12	13	14	15	16	17	18	19	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
50	2180	2225	2260	2314	2360	2426
52	2100	2235	2270	2325	2370	2437
54	2200	2245	2280	2330	2380	2447
56	2211	2256	2291	2346	2391	2453
58	2221	2266	2301	2356	2401	2463
60	2232	2277	2321	2366	2412	2479	2526	2586
62	2245	2287	2332	2377	2422	2489	2537	2596
64	2253	2298	2342	2387	2432	2499	2547	2607
66	2263	2308	2353	2398	2443	2500	2558	2617
68	2273	2319	2363	2408	2453	2510	2568	2628
70	2284	2329	2374	2419	2464	2521	2578	2638
72	2294	2339	2384	2429	2474	2531	2587	2646
74	2305	2350	2395	2440	2485	2542	2599	2659
76	2315	2360	2405	2450	2495	2552	2609	2670
78	2325	2371	2416	2461	2506	2563	2620	2680
80	2336	2381	2426	2471	2516	2573	2630	2690	2755	2814	2900	2945	2985	3023	3061	3102	3052	3001	2951	2900	2850	2788	2707	2657	2545	2495	2444	2394	2343	2292	2242
82	2346	2391	2436	2482	2527	2584	2641	2701	2765	2824	2910	2960	3000	3044	3081	3123	3072	3021	2971	2921	2870	2829	2779	2729	2667	2590	2516	2465	2414	2363	2313
84	2357	2402	2447	2493	2538	2594	2651	2711	2775	2834	2920	2976	3026	3064	3101	3143	3092	3041	2991	2941	2890	2849	2799	2749	2688	2613	2539	2488	2437	2386	2335
86	2367	2412	2457	2502	2548	2605	2662	2722	2786	2845	2936	3000	3058	3104	3141	3183	3132	3081	3031	2980	2930	2880	2830	2780	2719	2645	2571	2520	2469	2418	2367
88	2378	2423	2468	2513	2558	2615	2672	2732	2796	2855	2949	3009	3067	3105	3143	3185	3134	3082	3031	2981	2931	2881	2831	2781	2720	2647	2573	2522	2471	2420	2369
90	2388	2433	2478	2523	2568	2626	2683	2743	2807	2866	2963	3026	3087	3125	3163	3206	3154	3103	3052	3002	2951	2900	2850	2800	2738	2665	2591	2540	2489	2438	2387
92	2399	2444	2489	2534	2579	2636	2693	2753	2817	2876	2976	3040	3103	3141	3179	3222	3170	3119	3068	3017	2966	2915	2864	2813	2751	2678	2604	2553	2502	2451	2400
94	2409	2454	2499	2544	2589	2646	2703	2763	2828	2887	2989	3054	3117	3155	3193	3236	3184	3133	3082	3031	2980	2929	2878	2827	2765	2692	2618	2567	2516	2465	2414
96	2419	2465	2510	2555	2600	2657	2714	2774	2838	2897	3000	3078	3143	3181	3219	3262	3210	3159	3108	3057	3006	2955	2904	2853	2791	2718	2644	2593	2542	2491	2440
98	2430	2475	2520	2565	2610	2667	2724	2784	2849	2908	3011	3095	3168	3206	3244	3287	3235	3184	3133	3082	3031	2980	2929	2878	2816	2743	2670	2619	2568	2517	2466
100	2440	2485	2531	2576	2621	2678	2735	2795	2860	2918	3020	3104	3178	3216	3254	3297	3245	3194	3143	3092	3041	2990	2939	2888	2826	2753	2680	2629	2578	2527	2476
102	2451	2496	2541	2586	2631	2688	2745	2805	2870	2929	3030	3114	3188	3226	3264	3307	3255	3204	3153	3103	3052	3002	2951	2900	2838	2765	2692	2641	2590	2539	2488
104	2461	2506	2551	2596	2641	2698	2755	2815	2880	2939	3040	3124	3208	3246	3284	3327	3275	3224	3173	3123	3072	3022	2971	2921	2859	2786	2713	2662	2611	2560	2509
106	2472	2517	2562	2607	2652	2709	2766	2826	2890	2949	3050	3134	3218	3256	3294	3337	3285	3234	3183	3133	3082	3031	2980	2929	2867	2794	2721	2670	2619	2568	2517
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110	2493	2538	2583	2628	2673	2730	2787	2847	2911	3000	3097	3182	3266	3304	3342	3385	3333	3282	3231	3180	3129	3078	3027	2976	2914	2841	2768	2717	2666	2615	2564
112	2503	2548	2593	2638	2683	2740	2797	2857	2921	3000	3097	3182	3266	3304	3342	3385	3333	3282	3231	3180	3129	3078	3027	2976	2914	2841	2768	2717	2666	2615	2564
114	2513	2558	2603	2648	2693	2750	2807	2867	2931	3010	3107	3192	3276	3314	3352	3395	3343	3292	3241	3190	3139	3088	3037	2986	2924	2851	2778	2727	2676	2625	2574
116	2524	2569	2614	2659	2704	2761	2818	2878	2942	3020	3117	3202	3286	3324	3362	3405	3353	3302	3251	3200	3149	3098	3047	2996	2934	2861	2788	2737	2686	2635	2584
118	2534	2579	2624	2669	2714	2771	2828	2888	2952	3030	3127	3212	3296	3334	3372	3415	3363	3312	3261	3210	3159	3108	3057	3006	2944	2871	2798	2747	2696	2645	2594
120	2545	2590	2635	2680	2725	2782	2839	2899	2963	3040	3137	3222	3306	3344	3382	3425	3373	3322	3271	3220	3169	3118	3067	3016	2954	2881	2808	2757	2706	2655	2604
122	2555	2600	2645	2690	2735	2792	2849	2909	2973	3050	3147	3232	3316	3354	3392	3435	3383	3332	3281	3230	3179	3128	3077	3026	2964	2891	2818	2767	2716	2665	2614
124	2566	2611	2656	2701	2746	2803	2860	2920	2984	3060	3157	3242	3326	3364	3402	3445	3393	3342	3291	3240	3189	3138	3087	3036	2974	2901	2828	2777	2726	2675	2624
126	2576	2621	2666	2711	2757	2814	2871	2931	2995	3070	3167	3252	3336	3374	3412	3455	3403	3352	3301	3250	3199	3148	3097	3046	2984	2911	2838	2787	2736	2685	2634
128	2587	2632	2677	2722	2767	2824	2881	2941	3005	3080	3177	3262	3346	3384	3422	3465	3413	3362	3311	3260	3209	3158	3107	3056	2994	2921	2848	2797	2746	2695	2644

130	2597	2612	2687	2732	2777	2834	2882	2952	3016	3105	3232	3373	3493	3531	3509	3458	3407	3357	3306	3256	3205	3155	3104	3053	3003	2952	2902	2851	2800	2750	2699
131	2603	2653	2698	2743	2788	2845	2902	2962	3026	3115	3244	3391	3513	3552	3529	3478	3428	3377	3327	3276	3226	3175	3124	3074	3023	2973	2922	2871	2821	2770	2720
132	2618	2663	2708	2753	2798	2855	2912	2973	3037	3126	3256	3409	3534	3572	3549	3489	3438	3387	3337	3286	3236	3185	3135	3084	3034	2983	2932	2881	2831	2780	2730
133	2628	2674	2719	2764	2809	2866	2923	2983	3047	3136	3266	3427	3554	3592	3570	3510	3459	3408	3358	3307	3256	3206	3155	3104	3054	3003	2953	2902	2851	2801	2750
134	2639	2684	2729	2774	2819	2876	2933	2993	3058	3147	3278	3436	3574	3613	3590	3539	3489	3438	3388	3337	3286	3236	3185	3135	3084	3034	2983	2933	2882	2831	2780
135	2649	2694	2739	2785	2830	2887	2944	3004	3068	3157	3294	3464	3595	3633	3610	3560	3509	3459	3408	3357	3307	3256	3206	3155	3104	3054	3003	2953	2902	2851	2801
136	2660	2705	2750	2795	2840	2897	2954	3014	3078	3167	3307	3482	3615	3653	3631	3580	3529	3479	3428	3378	3327	3277	3226	3175	3125	3074	3024	2973	2923	2872	2821
137	2670	2715	2760	2805	2851	2908	2965	3025	3089	3178	3319	3501	3635	3674	3651	3600	3549	3498	3448	3398	3347	3297	3246	3196	3145	3094	3044	2993	2943	2892	2842
138	2681	2726	2771	2816	2861	2918	2975	3035	3100	3188	3331	3519	3655	3694	3671	3621	3570	3520	3469	3418	3368	3317	3267	3216	3165	3115	3064	3014	2963	2912	2862
139	2691	2736	2781	2826	2871	2928	2986	3046	3110	3199	3344	3537	3676	3714	3692	3641	3590	3540	3489	3439	3388	3337	3287	3236	3186	3135	3085	3034	2984	2933	2882
140	2702	2747	2792	2837	2882	2939	2996	3055	3120	3209	3356	3556	3696	3735	3712	3661	3611	3560	3510	3459	3408	3358	3307	3257	3206	3156	3105	3055	3004	2953	2903
141	2712	2757	2802	2847	2892	2949	3006	3067	3131	3221	3368	3575	3716	3755	3732	3682	3631	3581	3530	3479	3429	3378	3328	3277	3227	3176	3126	3075	3024	2973	2923
142	2722	2767	2812	2857	2902	2959	3016	3077	3141	3232	3379	3589	3730	3769	3746	3696	3645	3595	3544	3493	3443	3392	3342	3291	3240	3190	3140	3090	3040	2990	2940
143	2733	2778	2823	2868	2913	2970	3027	3087	3152	3243	3391	3614	3757	3796	3773	3722	3672	3621	3571	3520	3469	3419	3368	3318	3267	3216	3166	3116	3065	3014	2963
144	2743	2788	2833	2878	2923	2981	3038	3097	3162	3254	3402	3633	3777	3816	3793	3743	3692	3641	3591	3540	3490	3440	3390	3340	3290	3240	3190	3140	3090	3040	2990
145	2754	2799	2844	2889	2934	2991	3048	3109	3172	3267	3415	3651	3798	3836	3814	3763	3712	3662	3611	3561	3510	3460	3410	3360	3310	3260	3210	3160	3110	3060	3010
146	2764	2809	2854	2899	2945	3002	3059	3119	3183	3278	3426	3663	3810	3848	3826	3775	3724	3673	3622	3571	3520	3470	3420	3370	3320	3270	3220	3170	3120	3070	3020
147	2775	2820	2865	2910	2955	3012	3069	3129	3193	3289	3439	3688	3835	3873	3851	3800	3753	3702	3652	3601	3551	3500	3450	3400	3350	3300	3250	3200	3150	3100	3050
148	2786	2831	2876	2921	2966	3023	3080	3140	3204	3300	3452	3706	3858	3897	3875	3824	3773	3723	3672	3622	3571	3520	3470	3420	3370	3320	3270	3220	3170	3120	3070
149	2796	2841	2886	2931	2976	3033	3090	3150	3214	3312	3464	3718	3870	3917	3895	3844	3794	3743	3692	3642	3591	3541	3490	3440	3390	3340	3290	3240	3190	3140	3090
150	2806	2851	2896	2941	2986	3043	3101	3161	3225	3324	3478	3732	3889	3938	3915	3865	3814	3763	3713	3662	3612	3561	3510	3460	3410	3360	3310	3260	3210	3160	3110
151	2816	2861	2906	2951	2996	3053	3111	3171	3235	3335	3491	3745	3902	3958	3935	3885	3835	3784	3733	3682	3632	3581	3531	3480	3430	3380	3330	3280	3230	3180	3130
152	2826	2871	2916	2961	3006	3063	3121	3181	3245	3345	3503	3757	3914	3978	3955	3905	3855	3804	3753	3703	3652	3602	3551	3501	3450	3400	3350	3300	3250	3200	3150
153	2836	2881	2926	2971	3016	3073	3131	3191	3255	3355	3515	3769	3926	3999	3976	3926	3875	3824	3774	3723	3672	3622	3571	3521	3470	3420	3370	3320	3270	3220	3170
154	2846	2891	2936	2981	3026	3083	3141	3201	3265	3365	3527	3781	3938	4011	3989	3939	3889	3838	3787	3737	3686	3636	3585	3535	3484	3434	3384	3334	3284	3234	3184
155	2856	2901	2946	2991	3036	3093	3151	3211	3275	3375	3539	3793	3950	4023	4001	3951	3901	3850	3800	3750	3700	3650	3600	3550	3500	3450	3400	3350	3300	3250	3200
156	2866	2911	2956	3001	3046	3103	3161	3221	3285	3385	3550	3803	3960	4033	4011	3961	3911	3860	3810	3760	3710	3660	3610	3560	3510	3460	3410	3360	3310	3260	3210
157	2876	2921	2966	3011	3056	3113	3171	3231	3295	3395	3561	3813	3970	4043	4021	3971	3921	3870	3820	3770	3720	3670	3620	3570	3520	3470	3420	3370	3320	3270	3220
158	2886	2931	2976	3021	3066	3123	3181	3241	3305	3405	3571	3823	3980	4053	4031	3981	3931	3880	3830	3780	3730	3680	3630	3580	3530	3480	3430	3380	3330	3280	3230
159	2896	2941	2986	3031	3076	3133	3191	3251	3315	3415	3581	3833	3990	4063	4041	3991	3941	3890	3840	3790	3740	3690	3640	3590	3540	3490	3440	3390	3340	3290	3240
160	2906	2951	2996	3041	3086	3143	3201	3261	3325	3425	3591	3843	4000	4073	4051	4001	3951	3900	3850	3800	3750	3700	3650	3600	3550	3500	3450	3400	3350	3300	3250
161	2916	2961	3006	3051	3096	3153	3211	3271	3335	3435	3601	3853	4010	4083	4061	4011	3961	3910	3860	3810	3760	3710	3660	3610	3560	3510	3460	3410	3360	3310	3260
162	2926	2971	3016	3061	3106	3163	3221	3281	3345	3445	3611	3863	4020	4093	4071	4021	3971	3920	3870	3820	3770	3720	3670	3620	3570	3520	3470	3420	3370	3320	3270
163	2936	2981	3026	3071	3116	3173	3231	3291	3355	3455	3621	3873	4030	4103	4081	4031	3981	3930	3880	3830	3780	3730	3680	3630	3580	3530	3480	3430	3380	3330	3280
164	2946	2991	3036	3081	3126	3183	3241	3301	3365	3465	3631	3883	4040	4113	4091	4041	3991	3940	3890	3840	3790	3740	3690	3640	3590	3540	3490	3440	3390	3340	3290
165	2956	3001	3046	3091	3136	3193	3251	3311	3375	3475	3641	3893	4050	4123	4101	4051	4001	3950	3900	3850	3800	3750	3700	3650	3600	3550	3500	3450	3400	3350	3300
166	2966	3011	3056	3101	3146	3203	3261	3321	3385	3485	3651	3903	4060	4133	4111	4061	4011	3960	3910	3860	3810	3760	3710	3660	3610	3560	3510	3460	3410	3360	3310
167	2976	3021	3066	3111	3156	3213	3271	3331	3395	3495	3661	3913	4070	4143	4121	4071	4021	3970	3920	3870	3820	3770	3720	3670	3620	3570	3520	3470	3420	3370	3320
168	2986	3031	3076	3121	3166	3223	3281	3341	3405	3505	3671	3923	4080	4153	4131	4081	4031	3980	3930	3880	3830	3780	3730	3680	3630	3580	3530	3480	3430	3380	3330
169	2996	3041	3086	3131	3176	3233	3291	3351	3415	3515	3681	3933	4090	4163	4141	4091	4041	3990	3940	3890	3840	3790	3740	3690	3640	3590	3540	3490	3440	3390	3340
170	3006	3051	3096	3141	3186	3243	3301	3361	3425	3525	3691	3943	4100	4173	4151	4101	4051	4000	3950	3900	3850	3800	3750	3700	3650	3600	3550	3500	3450	3400	3350
171	3016	3061	3106	3151	3196	3253	3311	3371	3435	3535	3701	3953	4110	4183	4161	4111	4061	4010	3960	3910	3860	3810	3760	3710	3660	3610	3560	3510	3460	3410	3360
172	3026	3071	3116	3161	3206	3263	3321	3381	3445	3545	3711	3963	4120	4193	4171	4121	4071														

TABLE II.—FEMALES. TWO-STEP EXERCISE TOLERANCE TEST.

CONNECTION FOR HEIGHT. Add 25 POUNDS FOR EVERY INCH ABOVE 5 FEET 4 INCHES AND SUBTRACT FOR EVERY INCH BELOW 5 FEET 4 INCHES.

Age in Years.

Weight	10	11	12	13	14	15	16	17	18	19	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
50	1987	1981	1974	1967	1961	1954
52	2012	2006	1999	1992	1986	1979
54	2037	2031	2024	2017	2011	2004
56	2062	2056	2049	2042	2036	2029
58	2087	2081	2074	2067	2061	2054
60	2112	2106	2099	2092	2086	2079	2073	2071
62	2137	2131	2124	2117	2111	2104	2098	2096
64	2162	2156	2149	2142	2136	2129	2123	2121
66	2187	2181	2174	2167	2161	2154	2148	2146
68	2212	2206	2199	2192	2186	2179	2173	2171
70	2237	2231	2224	2217	2211	2204	2198	2196	2232	2233
72	2262	2256	2249	2242	2236	2229	2223	2221	2257	2258
74	2287	2281	2274	2267	2261	2254	2248	2246	2282	2283
76	2312	2306	2299	2292	2286	2279	2273	2271	2307	2308
78	2337	2331	2324	2317	2311	2304	2298	2296	2332	2333
80	2362	2356	2349	2342	2336	2329	2323	2321	2357	2358	2446	2580	2648	2672	2668	2668	2642	2616	2580	2564	2538	2511	2485	2459	2433	2407	2381	2355	2329	2303	2277
82	2387	2381	2374	2367	2361	2354	2348	2346	2380	2381	2466	2595	2661	2685	2682	2682	2656	2630	2593	2567	2540	2514	2488	2462	2436	2410	2384	2358	2332	2306	2280
84	2412	2406	2399	2392	2386	2379	2373	2371	2403	2404	2486	2610	2674	2698	2695	2695	2669	2643	2606	2580	2554	2528	2502	2476	2450	2424	2398	2372	2346	2320	2294
86	2437	2431	2424	2417	2411	2404	2398	2396	2426	2427	2506	2625	2687	2705	2697	2697	2671	2645	2608	2582	2556	2530	2504	2478	2452	2426	2400	2374	2348	2322	2296
88	2462	2456	2449	2442	2436	2429	2423	2422	2449	2450	2526	2640	2700	2717	2707	2707	2681	2655	2618	2592	2566	2540	2514	2488	2462	2436	2410	2384	2358	2332	2306
90	2487	2481	2474	2467	2461	2454	2448	2447	2472	2473	2548	2665	2725	2742	2732	2732	2706	2680	2643	2617	2591	2565	2539	2513	2487	2461	2435	2409	2383	2357	2331
92	2512	2506	2499	2492	2486	2479	2473	2472	2497	2498	2566	2677	2737	2754	2744	2744	2718	2692	2655	2629	2603	2577	2551	2525	2499	2473	2447	2421	2395	2369	2343
94	2537	2531	2524	2517	2511	2504	2498	2497	2518	2519	2586	2695	2755	2772	2762	2762	2736	2710	2673	2647	2621	2595	2569	2543	2517	2491	2465	2439	2413	2387	2361
96	2562	2556	2549	2542	2536	2529	2523	2522	2541	2542	2606	2705	2765	2782	2772	2772	2746	2720	2683	2657	2631	2605	2579	2553	2527	2501	2475	2449	2423	2397	2371
98	2587	2581	2574	2567	2561	2554	2548	2547	2568	2569	2626	2725	2785	2802	2792	2792	2766	2740	2703	2677	2651	2625	2599	2573	2547	2521	2495	2469	2443	2417	2391
100	2612	2606	2599	2592	2586	2579	2573	2572	2593	2594	2646	2745	2805	2822	2812	2812	2786	2760	2723	2697	2671	2645	2619	2593	2567	2541	2515	2489	2463	2437	2411
102	2637	2631	2624	2617	2611	2604	2598	2597	2618	2619	2666	2765	2825	2842	2832	2832	2806	2780	2743	2717	2691	2665	2639	2613	2587	2561	2535	2509	2483	2457	2431
104	2662	2656	2649	2642	2636	2629	2623	2622	2643	2644	2686	2785	2845	2862	2852	2852	2826	2800	2763	2737	2711	2685	2659	2633	2607	2581	2555	2529	2503	2477	2451
106	2687	2681	2674	2667	2661	2654	2648	2647	2668	2669	2706	2805	2865	2882	2872	2872	2846	2820	2783	2757	2731	2705	2679	2653	2627	2601	2575	2549	2523	2497	2471
108	2712	2706	2699	2692	2686	2679	2673	2672	2693	2694	2726	2825	2885	2902	2892	2892	2866	2840	2803	2777	2751	2725	2699	2673	2647	2621	2595	2569	2543	2517	2491
110	2737	2730	2724	2717	2711	2704	2698	2697	2718	2719	2746	2845	2905	2922	2912	2912	2886	2860	2823	2797	2771	2745	2719	2693	2667	2641	2615	2589	2563	2537	2511
112	2762	2755	2749	2742	2736	2729	2723	2722	2743	2744	2766	2865	2925	2942	2932	2932	2906	2880	2843	2817	2791	2765	2739	2713	2687	2661	2635	2609	2583	2557	2531
114	2787	2780	2774	2767	2761	2754	2748	2747	2768	2769	2792	2891	2951	2968	2958	2958	2932	2906	2869	2843	2817	2791	2765	2739	2713	2687	2661	2635	2609	2583	2557
116	2812	2805	2799	2792	2786	2779	2773	2772	2793	2794	2816	2915	2975	2992	2982	2982	2956	2930	2893	2867	2841	2815	2789	2763	2737	2711	2685	2659	2633	2607	2581
118	2837	2830	2824	2817	2811	2804	2798	2797	2818	2819	2840	2939	2999	3016	3006	3006	2980	2954	2917	2891	2865	2839	2813	2787	2761	2735	2709	2683	2657	2631	2605

120	2863	2855	2847	2840	2828	2817	2807	2808	2828	2838	2846	2853	2897	2801	2864	2835	2812	2782	2760	2734	2708	2682	2656	2630	2604	2577	2551	2525	2500	2473	2447
121	2888	2879	2870	2863	2845	2834	2826	2825	2846	2855	2863	2900	2914	2906	2878	2860	2823	2796	2770	2744	2718	2692	2666	2639	2613	2587	2561	2535	2509	2483	2457
122	2909	2902	2891	2884	2863	2851	2849	2842	2863	2872	2880	2918	2932	2922	2892	2862	2834	2806	2780	2754	2728	2701	2675	2649	2623	2597	2571	2545	2519	2493	2467
123	2932	2925	2908	2891	2873	2866	2859	2850	2869	2878	2887	2925	2939	2929	2898	2867	2838	2811	2785	2759	2733	2706	2680	2654	2628	2602	2576	2550	2524	2498	2472
124	2952	2945	2924	2903	2882	2873	2866	2859	2877	2886	2895	2934	2948	2938	2907	2876	2847	2820	2794	2768	2742	2715	2689	2663	2637	2611	2585	2559	2533	2507	2481
125	2972	2965	2944	2923	2902	2893	2886	2879	2897	2906	2915	2954	2968	2958	2927	2896	2867	2840	2814	2788	2762	2736	2710	2684	2658	2632	2606	2580	2554	2528	2502
126	2992	2985	2964	2943	2922	2913	2906	2899	2917	2926	2935	2974	2988	2978	2947	2916	2887	2860	2834	2808	2782	2756	2730	2704	2678	2652	2626	2600	2574	2548	2522
127	3012	3005	2984	2963	2942	2933	2926	2919	2937	2946	2955	2994	3008	2998	2967	2936	2907	2880	2854	2828	2802	2776	2750	2724	2698	2672	2646	2620	2594	2568	2542
128	3032	3025	3004	2983	2962	2953	2946	2939	2957	2966	2975	3014	3028	3018	2987	2956	2927	2898	2872	2846	2820	2794	2768	2742	2716	2690	2664	2638	2612	2586	2560
129	3052	3045	3024	3003	2982	2973	2966	2959	2977	2986	2995	3034	3048	3038	3007	2976	2947	2918	2892	2866	2840	2814	2788	2762	2736	2710	2684	2658	2632	2606	2580
130	3072	3065	3044	3023	3002	2993	2986	2979	2997	3006	3015	3054	3068	3058	3027	2996	2967	2938	2912	2886	2860	2834	2808	2782	2756	2730	2704	2678	2652	2626	2600
131	3092	3085	3064	3043	3022	3013	3006	2999	3017	3026	3035	3074	3088	3078	3047	3016	2987	2960	2934	2908	2882	2856	2830	2804	2778	2752	2726	2700	2674	2648	2622
132	3112	3105	3084	3063	3042	3033	3026	3019	3037	3046	3055	3094	3108	3098	3067	3036	3007	2978	2952	2926	2900	2874	2848	2822	2796	2770	2744	2718	2692	2666	2640
133	3132	3125	3104	3083	3062	3053	3046	3039	3057	3066	3075	3114	3128	3118	3087	3056	3027	2998	2972	2946	2920	2894	2868	2842	2816	2790	2764	2738	2712	2686	2660
134	3152	3145	3124	3103	3082	3073	3066	3059	3077	3086	3095	3134	3148	3138	3107	3076	3047	3018	2992	2966	2940	2914	2888	2862	2836	2810	2784	2758	2732	2706	2680
135	3172	3165	3144	3123	3102	3093	3086	3079	3097	3106	3115	3154	3168	3158	3127	3096	3067	3038	3012	2986	2960	2934	2908	2882	2856	2830	2804	2778	2752	2726	2700
136	3192	3185	3164	3143	3122	3113	3106	3099	3117	3126	3135	3174	3188	3178	3147	3116	3087	3060	3034	3008	2982	2956	2930	2904	2878	2852	2826	2800	2774	2748	2722
137	3212	3205	3184	3163	3142	3133	3126	3119	3137	3146	3155	3194	3208	3198	3167	3136	3107	3078	3052	3026	3000	2974	2948	2922	2896	2870	2844	2818	2792	2766	2740
138	3232	3225	3204	3183	3162	3153	3146	3139	3157	3166	3175	3214	3228	3218	3187	3156	3127	3098	3072	3046	3020	2994	2968	2942	2916	2890	2864	2838	2812	2786	2760
139	3252	3245	3224	3203	3182	3173	3166	3159	3177	3186	3195	3234	3248	3238	3207	3176	3147	3118	3092	3066	3040	3014	2988	2962	2936	2910	2884	2858	2832	2806	2780
140	3272	3265	3244	3223	3202	3193	3186	3179	3197	3206	3215	3254	3268	3258	3227	3196	3167	3138	3112	3086	3060	3034	3008	2982	2956	2930	2904	2878	2852	2826	2800
141	3292	3285	3264	3243	3222	3213	3206	3199	3217	3226	3235	3274	3288	3278	3247	3216	3187	3160	3134	3108	3082	3056	3030	3004	2978	2952	2926	2900	2874	2848	2822
142	3312	3305	3284	3263	3242	3233	3226	3219	3237	3246	3255	3294	3308	3298	3267	3236	3207	3178	3152	3126	3100	3074	3048	3022	2996	2970	2944	2918	2892	2866	2840
143	3332	3325	3304	3283	3262	3253	3246	3239	3257	3266	3275	3314	3328	3318	3287	3256	3227	3198	3172	3146	3120	3094	3068	3042	3016	2990	2964	2938	2912	2886	2860
144	3352	3345	3324	3303	3282	3273	3266	3259	3277	3286	3295	3334	3348	3338	3307	3276	3247	3218	3192	3166	3140	3114	3088	3062	3036	3010	2984	2958	2932	2906	2880
145	3372	3365	3344	3323	3302	3293	3286	3279	3297	3306	3315	3354	3368	3358	3327	3296	3267	3238	3212	3186	3160	3134	3108	3082	3056	3030	3004	2978	2952	2926	2900
146	3392	3385	3364	3343	3322	3313	3306	3299	3317	3326	3335	3374	3388	3378	3347	3316	3287	3258	3232	3206	3180	3154	3128	3102	3076	3050	3024	2998	2972	2946	2920
147	3412	3405	3384	3363	3342	3333	3326	3319	3337	3346	3355	3394	3408	3398	3367	3336	3307	3278	3252	3226	3200	3174	3148	3122	3096	3070	3044	3018	2992	2966	2940
148	3432	3425	3404	3383	3362	3353	3346	3339	3357	3366	3375	3414	3428	3418	3387	3356	3327	3298	3272	3246	3220	3194	3168	3142	3116	3090	3064	3038	3012	2986	2960
149	3452	3445	3424	3403	3382	3373	3366	3359	3377	3386	3395	3434	3448	3438	3407	3376	3347	3318	3292	3266	3240	3214	3188	3162	3136	3110	3084	3058	3032	3006	2980
150	3472	3465	3444	3423	3402	3393	3386	3379	3397	3406	3415	3454	3468	3458	3427	3396	3367	3338	3312	3286	3260	3234	3208	3182	3156	3130	3104	3078	3052	3026	3000
151	3492	3485	3464	3443	3422	3413	3406	3399	3417	3426	3435	3474	3488	3478	3447	3416	3387	3358	3332	3306	3280	3254	3228	3202	3176	3150	3124	3098	3072	3046	3020
152	3512	3505	3484	3463	3442	3433	3426	3419	3437	3446	3455	3494	3508	3498	3467	3436	3407	3378	3352	3326	3300	3274	3248	3222	3196	3170	3144	3118	3092	3066	3040
153	3532	3525	3504	3483	3462	3453	3446	3439	3457	3466	3475	3514	3528	3518	3487	3456	3427	3398	3372	3346	3320	3294	3268	3242	3216	3190	3164	3138	3112	3086	3060
154	3552	3545	3524	3503	3482	3473	3466	3459	3477	3486	3495	3534	3548	3538	3507	3476	3447	3418	3392	3366	3340	3314	3288	3262	3236	3210	3184	3158	3132	3106	3080
155	3572	3565	3544	3523	3502	3493	3486	3479	3497	3506	3515	3554	3568	3558	3527	3496	3467	3438	3412	3386	3360	3334	3308	3282	3256	3230	3204	3178	3152	3126	3100
156	3592	3585	3564	3543	3522	3513	3506	3499	3517	3526	3535	3574	3588	3578	3547	3516	3487	3458	3432	3406	3380	3354	3328	3302	3276	3250	3224	3198	3172	3146	3120
157	3612	3605	3584	3563	3542	3533	3526	3519	3537	3546	3555	3594	3608	3598	3567	3536	3507	3478	3452	3426	3400	3374	3348	3322	3296	3270	3244	3218	3192	3166	3140
158	3632	3625	3604	3583	3562	3553	3546	3539	3557	3566	3575	3614	3628	3618	3587	3556	3527	3498	3472	3446	3420	3394	3368	3342	3316	3290	3264	3238	3212	3186	3160
159	3652	3645	3624	3603	3582	3573	3566	3559	3577	3586	3595	3634	3648	3638	3607	3576	3547	3518	3492	3466	3440	3414	3388	3362	3336	3310	3284	3258	3232	3206	3180
160	3672	3665	3644	3623	3602	3593	3586	3579	3597	3606	3615	3654	3668	3658	3627	3596	3567	3538	3512	3486	3460	3434	3408	3382	3356	3330	3304	3278	3252	3226	3200
161	3692	3685	3664	3643	3622	3613	3606	3599	3617	3626	3635	3674	3688	3678	3647	3616	3587	3558	3532	3506	3480	3454	3428	3402	3376	3350	3324	3298	3272	3246	3220
162	3712	3705	3684	3663	3642	3633	3626	3619	3637																						

Thus for a boy, aged fourteen years, weighing 104 pounds the table will show a figure of 2642 foot-pounds. A height, let us say, of 5 feet 5 inches means 1 inch above the standard 5 feet 4 inches and therefore an addition of 50 foot-pounds, giving a total of 2692. A woman, aged forty-seven years, weighing 130 pounds, and 5 feet 2 inches tall, should be able to perform 2616 foot-pounds of work. That is, taking the mean between the figures for forty-six and forty-eight years, we obtain 2666 by age and weight from the table, then deduct 2 by 25, or 50, as a correction for a height 2 inches below the standard, giving a total of 2616 foot-pounds.

A deviation of 10 per cent in either direction may be regarded as still within normal limits.

Method of Performing Test. The steps (Fig. 1), a watch—preferably a stop-watch—and a blood-pressure instrument are all the apparatus required. Correct figures for the patient's height, weight and age are ascertained, and the normal number of foot-pounds of work to be expected are obtained from the tables as described above. This number is divided by the patient's weight, the quotient being the number of ascents he should make in a minute and a half. Thus a boy, aged fourteen years, as noted above, weighing 104 pounds and five feet five in height would be expected from the tables to do 2692 foot-pounds of work: he should, therefore, make

$$\frac{2692}{104}$$

$$26$$

or 26 ascents. The patient is seated, and rests until his pulse and blood pressure fall no lower, as indicated by repeated observations (Fig. 2). This may require from three to five minutes. The blood-pressure cuff is allowed to remain on the arm, and the patient stands ready in front of the steps. At a given signal, the exact time being carefully noted, and most conveniently taken at a whole or half minute, he ascends the steps. He descends on the other side, and returns, ascending the steps again and descending to his original starting point. This is repeated until his allotted number of ascents has been completed in the one and a half minutes (Figs. 3 to 12). The turn before each ascent should always be made toward the same side of the room, to insure an alternation of turn to right and left. This is to prevent giddiness or vertigo, factors which produce marked changes in pulse and blood pressure. The patient is kept to the correct rate of stair climbing by observation of the time during the exercise, his rate being accelerated or retarded as may be necessary to complete his quota of ascents in the allotted time. Our procedure has been to allow the last five or six seconds of the exercise time for the subject to resume his seat. Blood pressure and pulse readings are then again taken as often as desired. If the individual is normal, and there is no complicating factor such as a cold, men-

strual period or headache, the pulse rate and blood pressure will return to normal within two minutes. Although we have watched for dyspnea, cyanosis and fatigue, we have found that this test causes few, if any signs of discomfort, since it involves merely an habitual activity. It is worthy of note, however, that in patients with valvular or muscular disease of the heart, these objective signs become very prominent.

A return of the pulse to a rate within five beats of that before exercise, and of the blood pressure to a level within 5 mm. of Hg. is accepted as a normal response.

Method for Obtaining Patient's Maximum Tolerance. If the blood pressure does not return to resting level within the two minutes the patient's tolerance is subnormal. If the exact exercise tolerance of the individual is desired, the test should be repeated using fewer ascents until a number is reached which permits a return within the prescribed time. On the other hand, if the blood pressure and pulse rate return to the resting level sooner than two minutes, the exercise tolerance is above average, and the number of ascents should be increased.

The product of the number of ascents by the weight of the individual gives the foot-pounds of work performed per minute.

By the careful use of this test the physician may discover the early stages of circulatory insufficiency, or may trace the progress of an organic condition of the heart or the degree of recovery from such an insufficiency. The quantitative information obtained may be used in giving advice as to general physical activity, or sports and games. The foot-pounds of work performed by patients with valvular or myocardial disease may be studied and the insufficiency thus graded.

Summary. The advantages of a quantitative method for an exercise tolerance test are described, and its value in diagnosis emphasized.

The test here described is an extremely simple one, utilizes habitual muscular movements, causing a minimum of excitement, and no dizziness or vertigo. It consists in ascending and descending two steps, each 9 inches high. The number of foot-pounds of work performed is easily calculated.

The criterion for the satisfactory performance of the test is a return of systolic blood pressure and of pulse rate to the preëxercise (resting) level within two minutes after the end of exercise.

Tables have been constructed giving foot-pounds of work per minute performed by normal individuals, with variations for sex, age, height and weight.

Curves of foot-pounds of work per minute, plotted against age, show that until about puberty girls perform more efficiently than boys, but after thirteen years males do better than females. The sharpest rise in the curve occurs between ten and twenty years of

age. Males reach a maximum of about 3795 foot-pounds of work at twenty-six to twenty-nine years, and women a maximum of 2950 at about twenty-four years. After these optimum ages a gradual but steady decline occurs.

Men at the optimum age have a work capacity of about $\frac{1}{8}$ horsepower, and women about $\frac{1}{11}$.

Exercise tolerance varies directly with body weight up to the optimum weight of 160 to 165 pounds for men, and 135 to 145 pounds for women. Beyond these weights the exercise tolerance falls.

The relation of work capacity to height is a direct one; the taller the individual the greater is his exercise tolerance.

The practical importance of the procedure is that the patient can be tested to determine: (1) whether his exercise tolerance is within normal limits, (2) what his actual maximal tolerance is in foot-pounds.

The test is helpful in the diagnosis and the grading of circulatory efficiency and insufficiency, and for tracing the changes arising therefrom during the progress of an organic condition of the heart, or during recovery. It may also be used in giving advice as to sports and games.

NOTE.—We wish to thank Dr. L. A. Conner for his interest in the progress of this paper and for his many helpful suggestions. We are indebted to the members of the faculty of Cornell University Medical College and to those of the College of the City of New York who volunteered to serve as controls. Dr. Paul Klapper, Dr. B. S. Oppenheimer, Dr. J. Lewengood, Mr. Harry Wittner and Miss Lydia Buechi have our sincere thanks for their coöperation and their help.

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APPENDIX.

Statistical Treatment of Data for Construction of Tables.

By F. C. CHILLRUD.

THE purpose of the statistical treatment of the data was to combine measurements to indicate best what one might expect the score in foot-pounds to be for the various combinations of height, weight and age in each of two groups (59 males and 56 females).

Partial correlation and regression equation technique was not applicable as a curvilinear relationship existed between age and each of the other

variables. A second or higher degree parabola was tried but abandoned. Finally, study of the various correlation tables resulted in breaking up each group into two parts, those below and those above twenty-one years of age, and using the ordinary partial and regression equation technique, which fitted fairly well for these straight lines. The resulting regression equations were:

Males, below twenty-one years of age, 22 cases. Foot-pounds = 54.4 (height) + 5.22 (weight) + 45.1 (age) - 2017 .

Males, above twenty-one years of age, 37 cases: Foot pounds = -4.8 (height) + 10.2 (weight) - 25.3 (age) + 3203 .

Females, below twenty-one years of age, 26 cases: Foot-pounds = 24.7 (height) + 12.5 (weight) - 6.59 (age) - 153 .

Females, above twenty-one years of age, 30 cases: Foot-pounds = 25.3 (height) + 4.9 (weight) - 13.0 (age) + 1022 .

To secure the values found in Tables I and II, 5 feet 4 inches was substituted for height in all of the above equations; they were then solved in foot-pounds for the varying values of weight and age specified in the tables. Discrepancies, however, were found between the values in the neighborhood of ages twenty and twenty-two years in the case of both tables, due to the fact that values for twenty years and below were calculated from one equation and those for twenty-two years and above from another. A smoothing process was employed to bring the two parts of each table together at this point.

The following table gives a summary of the means, standard deviations and correlation coefficients obtained in the case of each of the four groups. The table also affords a comparison of the standard deviation of foot-pounds in the case of each group with the standard error of estimate in predicting foot-pounds from a combination of measurements of height, weight and age. In order to conserve space, no figures for probable errors of the means, standard deviations and correlation coefficients are included.

Means.

Means.	Males.		Females.	
	Below 21.	Above 21.	Below 21.	Above 21.
Foot-pounds	2815.0	3430.0	2331.0	2810.0
Height	64.7	68.2	57.4	64.4
Weight	119.8	156.7	92.4	129.8
Age	15.1	40.6	13.7	36.6

Standard Deviations.

Foot-pounds	522.0	514.7	379.5	350.0
Height	4.56	2.77	4.0	2.91
Weight	23.2	13.8	17.4	17.1
Age	2.36	13.0	2.22	10.3

Correlation Coefficients.

Foot-pounds and height	0.847	0.241	0.722	0.393
Foot-pounds and weight	0.802	0.257	0.765	0.270
Foot-pounds and age	0.770	-.632	0.645	-.383
Height and weight .	0.877	0.483	0.863	0.456
Height and age . .	0.825	-.211	0.819	-.192
Weight and age . .	0.751	0.006	0.823	0.172
Standard deviation (foot-pounds) . .	522.0	515.0	379.0	350.0
Standard error of estimate in predicting foot-pounds . . .	263.0	375.0	240.0	294.0

THE WATER BALANCE IN CARDIAC DECOMPENSATION.

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EDEMA is one of the outstanding signs of decompensation. Loeb¹ has thus summarized the present status of the knowledge of this circumstance: "Dilatation of the capillaries and veins due to the faulty functioning of the circulation is the principal cause of the increased transudation and the subsequent edema in cardiac decompensation, but there may perhaps be in addition an increased filtration pressure responsible for these results. The vascular dilatation is apparently followed by an increased permeability of the capillaries and by a movement of sodium chlorid and water in the direction from the blood to the tissues. Retention of sodium chlorid plays a rôle also in the case of cardiac edema, although it is a smaller one than in the case of renal edema. In certain stages of cardiac edema a hydremia seems to occur. As to the occurrence of a true plethora, the statements are contradictory. In addition to the increased transudation, there is a delayed absorption and an alteration in the relations determining the exchange of fluid between tissues and blood vessels. Experimentally produced myocarditic lesions may give rise to a lowering of blood pressure and a diminution in the amount of urine under certain conditions, but so far it has not been possible to influence by this experimental method the amount of edematous fluid."

The importance of the kidney in the elimination of the edematous fluid is clearly admitted. The work of Richards² established the changes in glomerular activity with variations in blood pressure and the existence of an optimal pressure for glomerular filtration. Furthermore, Clark³ and Eyster and Middleton⁴ determined a definite relationship between venous pressure and urinary output in certain cases of cardiac decompensation. As the venous pressure falls, diuresis ensues and *vice versa*. This inverse ratio of venous pressure to urinary output is by no means constant, but its occurrence is frequent enough to arrest the attention. Sollmann's observation⁵ of a probable obliteration of the filtration space in Bowman's capsule on the elevation of the venous pressure may supplement the earlier explanation of a compression of the tubules. His pressure readings, however, exceed the limits of clinical observation in the peripheral veins.

With such significant circulatory relationships, the kidney occupies an important position in reflecting the cardiovascular competency.

It has, of course, been remarked that the water balance gives valuable information in cardiac decompensation, but the prognostic importance of its routine study is not generally recognized in practice. Obviously, the fluid intake and the fluid lost by other channels than the kidneys will directly affect the urinary output. Beyond this, Addis and Watanabe⁶ showed a surprising range of urinary output in different individuals on a fixed fluid intake, and indeed in the same person on different days or in different parts of the same day. From many sources Weir, Larson and Rowntree⁷ adduced the following figures for the average intake and urinary output of fluids:

Intake	2290 to 3700 cc.
Urinary output	1500 to 2000 cc. (65 to 54 per cent).

It may be stated then that the urinary output represents approximately 60 per cent of the fluid intake. This figure is of necessity a very arbitrary one: and subject to the loosest construction, any increase of the output above this point may be termed diuresis.

TABLE I.—DAILY DISTRIBUTION OF THE DECOMPENSATED CASES ACCORDING TO OUTPUT-INTAKE FIGURES.

Days . . .		1.		2.		3.		4.		5.		6.		7.		8.		9.	
Termination .		S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Output-intake ratio.	100%	6	5	5	10	12	10	15	7	15	10	12	7	12	8	14	7	7	4
	80	1	4	2	3	3	3	4	5	3	6	6	2	4	5	4	7	3	3
	60	4	4	8	5	7	3	7	6	5	4	6	8	9	8	8	4	14	8
	40	4	6	6	5	8	8	7	10	8	10	6	11	8	8	6	7	5	9
	20	5	4	6	8	7	5	5	6	7	4	8	3	2	7	7	7	6	5
	1	0	7	0	3	1	5	1	2	2	4	0	4	1	2	2	2	2	3

S., surviving; D., dying.

(Continued.)

Days . . .		10.		11.		12.		13.		14.		15.		16.		17.		18.	
Termination .		S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Output-intake ratio.	100%	5	6	10	5	3	4	7	3	8	3	7	4	5	3	4	4	5	3
	80	6	2	3	2	5	1	6	2	7	3	3	3	2	0	6	1	5	2
	60	12	5	9	8	10	7	6	7	10	3	11	5	13	6	10	1	7	2
	40	8	8	5	6	10	10	10	8	8	8	11	4	7	4	10	9	7	6
	20	4	6	6	4	6	1	8	4	3	6	3	7	4	4	3	4	6	2
	1	2	3	6	4	1	3	0	2	3	0	0	1	2	4	0	1	2	1

S., surviving; D., dying.

As a matter of routine the fluid intake and output of all decompensated cardiac cases have been charted since the opening of the Wisconsin General Hospital in 1924. The Karell diet modified to include 36 ounces (1080 cc.) of milk daily is the common order on admission. No effort has been made to estimate the amount of fluid derived from other food added from time to time since a clinical procedure available to the general practitioner is sought. Unfor-

TABLE II.—ANALYSIS OF THE WATER BALANCE IN CARDIAC DECOMPENSATION.

Day	1.		2.		3.		4.		5.		6.	
	S.		D.		S.		D.		S.		D.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Termination												
Average intake ratio	11	55.0	13	43.3	15	55.0	18	52.9	22	57.8	16	47.0
Below 60%	9	45.0	17	56.6	12	45.0	16	47.0	20	57.5	23	50.0
11.												
Day	7.		8.		9.		10.		11.		12.	
	S.		D.		S.		D.		S.		D.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Termination												
Average intake ratio	25	69.4	21	55.2	26	65.0	18	52.9	24	64.8	15	40.8
Below 60%	11	30.5	17	44.7	14	35.0	16	47.0	13	35.1	17	53.1
16.												
Day	13.		14.		15.		16.		17.		18.	
	S.		D.		S.		D.		S.		D.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Termination												
Average intake ratio	19	51.3	12	46.1	25	64.1	9	39.1	21	60.0	12	50.0
Below 60%	18	48.6	14	53.8	14	35.8	14	60.8	14	40.0	12	50.0

S., surviving; D., dying.

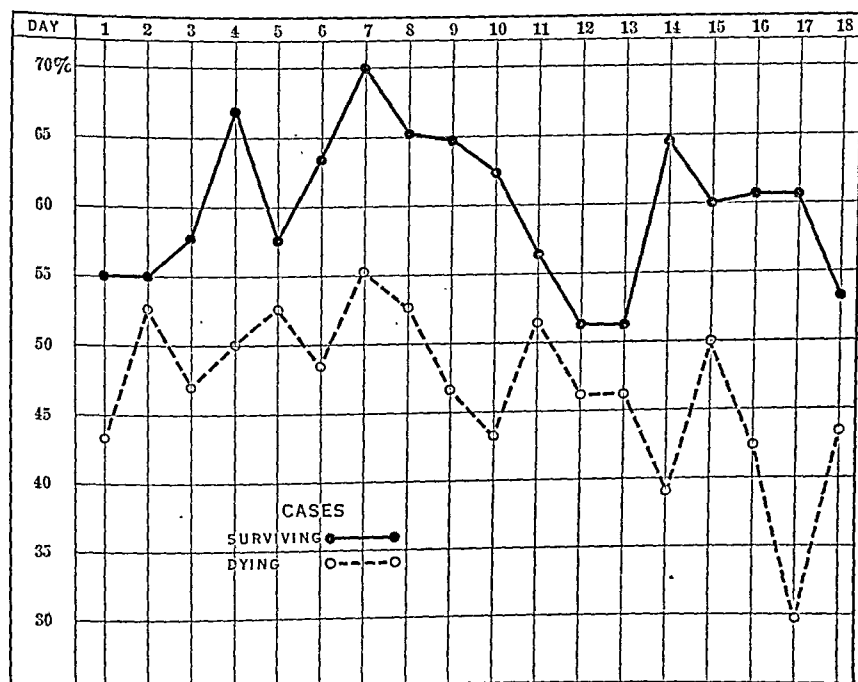
tunately, no scales have been available to add the further data of weight changes in these bed cases. A total of 108 instances of cardiac decompensation with adequate data for the present purposes has been studied in that period. They lend themselves readily to the following division:

	Surviving.	Dying.
Edematous	46	45
Nonedematous	13	4
	<hr/> 59	<hr/> 49

For the study of the water balance the edematous cases (91) alone have been considered.

In Table I, the actual number of cases falling under the various output-intake ratios is entered for each of the first eighteen days of hospitalization. In Table II, these cases have been gathered into two groups, those showing above 60 per cent output and those below 60 per cent, the arbitrary level of diuresis. To clarify further these figures the percentages are stated for the surviving and the dying groups on the separate days. Chart I reduces these percentage figures

CHART I.



to a graph in which the proportions of the studied cases of the two groups showing diuresis on the several days are plotted. Strikingly the fatal group shows a majority of its components exceeding the 60 per cent output-intake figure on but seven of the eighteen days, whereas the surviving group showed a constant majority with diuresis for any given day. Attention is directed to the rough

similarity of the form of the two curves in the first thirteen days of residence. In this period, six of the seven days of preponderance of diuresis in the fatal group occurred. In both groups, the curves have an upward swing in the first week and thereafter a sharp decline. With the close of the second week and the beginning of the third week the curves diverge.

These data indicate a distinct tendency for a primary diuresis in all cases of decompensation with edema under the circumstances of hospital care. This tendency is less marked and less sustained in the fatal group. Occasionally the primary period of diuresis does not make its appearance in the fatal cases, and in only a few instances is the curve of output-intake maintained at a satisfactory level in this group. As a rule even the surviving cases show a slump in the curve of diuresis after the primary rise, but characteristically there is an early recovery of a sound output-intake ratio. Clearly no arbitrary rules based on the available data are admissible. Nevertheless a simple and safe barometer of circulatory efficiency is offered in the study of the water balance in cardiac decompensation.

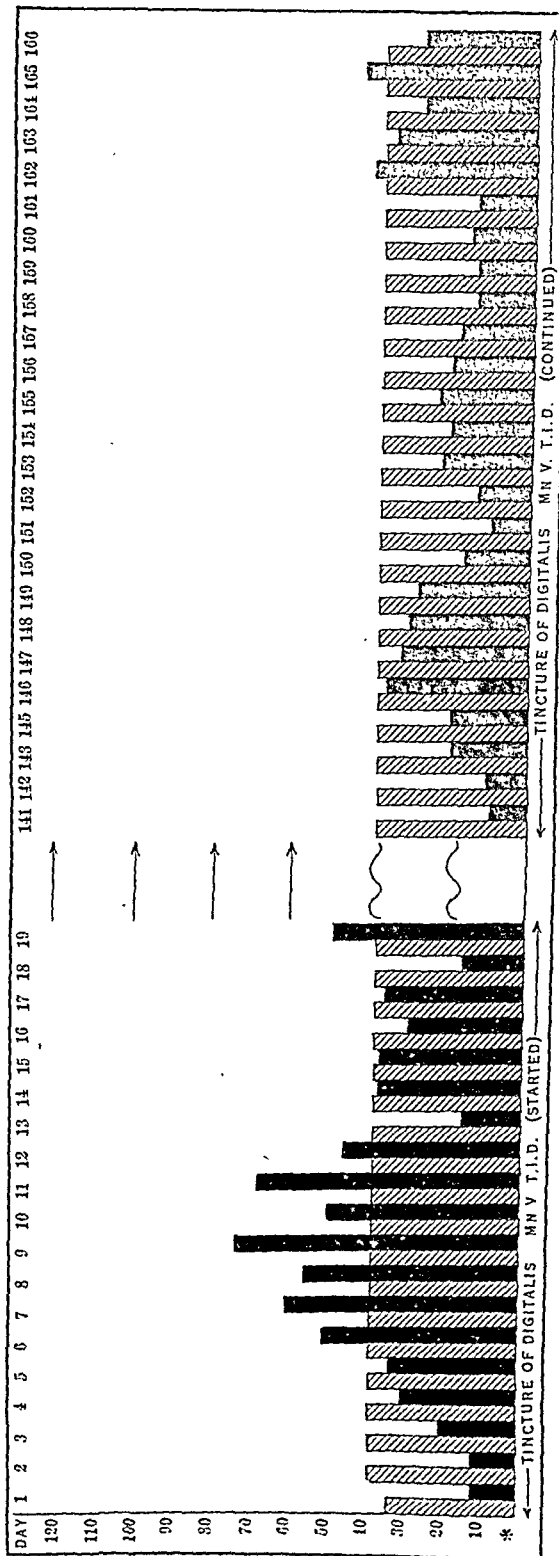
Two characteristic curves of water balance are presented for contrast.

Case Reports.—CASE I (2807), a white school-boy, aged nineteen years, presented the picture of cardiac decompensation in cough, palpitation, extrasystolic arrhythmia, general anasarca, pulmonary congestion and hepatic engorgement. The occasion of his admission was this exacerbation of cardiac incompetency, which had originally dated back to his eleventh year when he had suffered from rheumatic fever. The heart showed double aortic and mitral lesions. With rest in bed, small doses of digitalis, fluid and salt restriction, an immediate and continued improvement was effected. The customary early positive water balance occurred (Chart II). An excellent output-intake ratio was maintained; and particular attention is directed to the wave like tendency of the output curve.

CASE II (5203), a white male, aged fifty-three years, farmer and well driller by occupation, presented the clinical picture of cardiac decompensation dependent upon myocardial degeneration. Influenza complicated by pneumonia eight months prior to admission was the precipitating factor, whereas arteriosclerosis appeared to be the only etiologic background. An arrhythmia proved to depend upon auricular flutter and right bundle-branch block. Edema advanced slowly and jaundice deepened. The development of coupled beats from extrasystoles under digitalis therapy led to its discontinuance on the thirtieth day. Significantly there never occurred a positive water balance in this case nor was the 60 per cent plus output-intake ratio exceeded except on one day (Chart III). Death ensued on the fifty-third day.

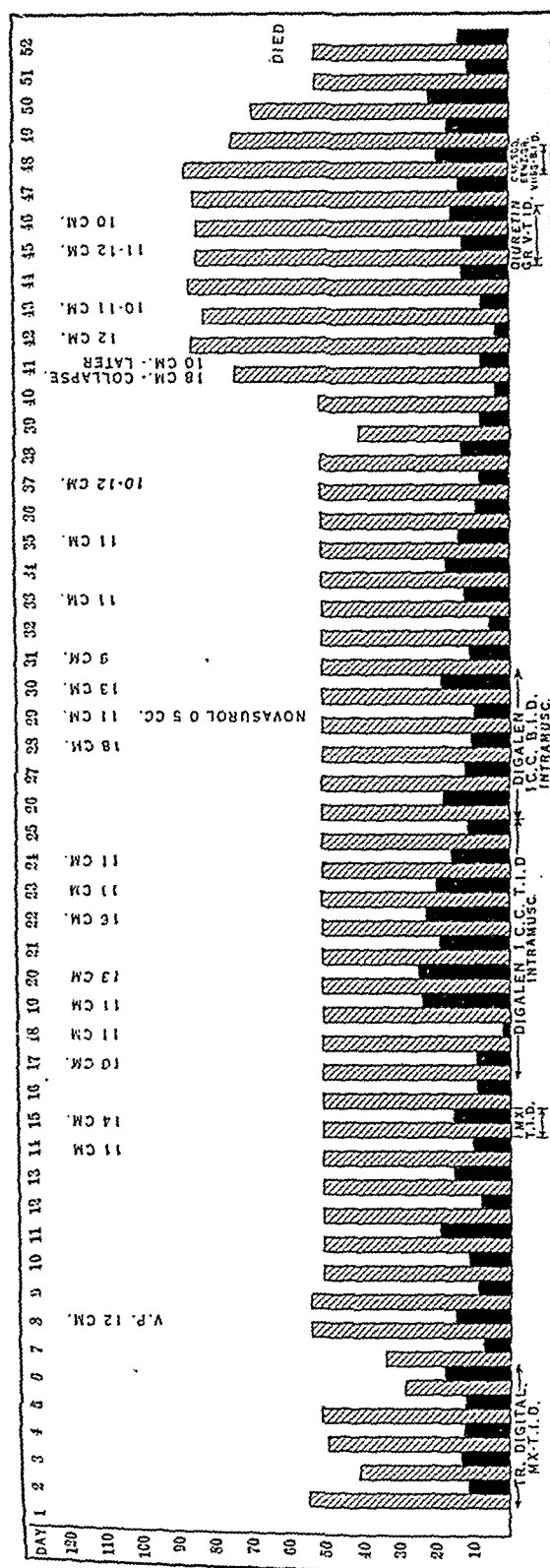
Factors Influencing Diuresis in Cardiac Decompensation. *Rest in Bed and Diet.* In conserving cardiac reserve and in exacting a minimum of myocardial energy, physical rest meets two primary indications for the treatment of decompensation. The French

CHART II.



* All volumes are given as fluid ounces; hatched columns represent intake; solid, output.

CHART III.



school has long supported the diagnostic difference in the nocturnal diuresis of cardiac and renal cases. In cases of cardiac decompensation, there occurs "a veritable dissociation in the elimination of the urinary water and chlorids," in that contrary to the nephritic the night urine is low in chlorids. (Vaquez⁸) Regardless of the factors concerned, diuresis with rest in bed is almost constant in the edematous cases of cardiac decompensation.

The importance of dietetic control in the management of the edema of decompensation has long been recognized. It has resolved itself into the restriction of the sodium chlorid and the water intake. Hippocrates⁹ recommended the following course in the treatment of dropsy: "The patient should eat dry and acrid things, for thus will he pass the more water, and his strength be kept up." Various modifications of the Karell regimen constitute the accustomed procedure. In the Wisconsin General Hospital, unless there be special contraindications, the decompensated patient is given 1000 to 1500 cc. of fluid daily on admission. As other articles of diet are added, the salt-poor restriction is enforced until water logging disappears. No effort is made to separate the results of rest in bed and the dietary restrictions. Particular attention is directed to the early period of diuresis with rest in bed and appropriate diet in evaluating the effect of any concurrent type of treatment. The following case illustrates this point:

CASE III (6075), a white male, aged forty-four years and a farmer by occupation, was first admitted on September 29, 1926, complaining of shortness of breath. Four years previously he had experienced an attack of precordial pain lasting a week; but evidences of circulatory incompetency first appeared with dyspnea and edema in 1923. Periodic exacerbations of the edema of the legs and scrotum have interfered with work from time to time. The only illness, other than the above mentioned, with a possible relation to the chief complaint, was influenza in 1918.

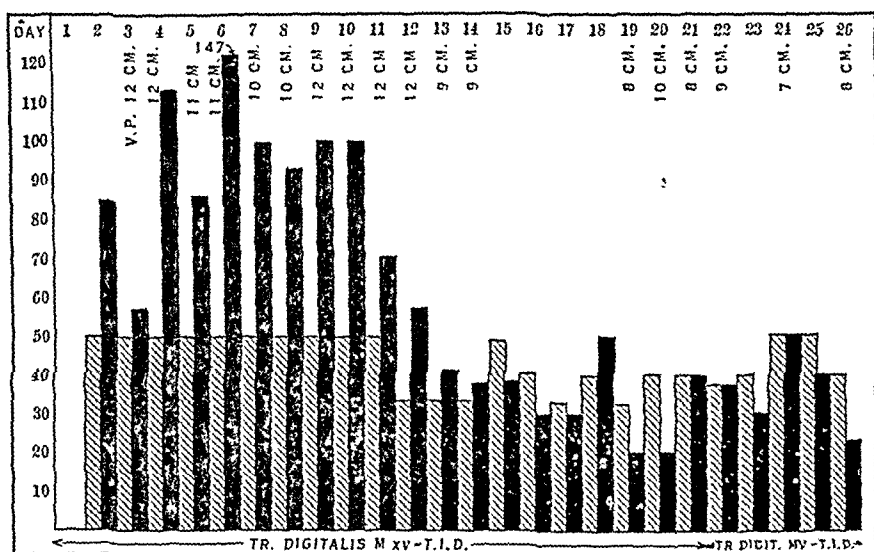
The physical examination established marked cyanosis, emphysematous type of chest, basal congestive râles, marked enlargement of the heart (particularly to the left), woody mitral first sound and accentuated pulmonic second sound, systolic blood pressure 134 mm., diastolic 60 mm., liver palpable and pulsating 8 cm. below the costal margin, spleen just palpable, marked edema of the legs and scrotum, positive centrifugal venous pulse. Laboratory examinations added nothing to the picture. No evidence could be gathered to substantiate the suspicion of an adherent pericardium.

A conclusion of cardiac decompensation depended upon myocardial degeneration was drawn. Significant were the evidences of tricuspid insufficiency. Under rest in bed, limitation of fluids (1500 cc.) and moderate doses of digitalis (Mxv, t.i.d.) there was quickly established a positive water balance (Chart IV) with coincident and progressive subsidence in the edema and other evidences of cardiac decompensation.

On two subsequent admissions, the same clinical situation pertained; but so dramatic had been the diuresis on the original observation that on both of these re-admissions the patient was simply put to bed on a salt-poor diet with a restriction of fluids to 1500 cc. Curves of diuresis comparable to that of the first admission were obtained in both instances

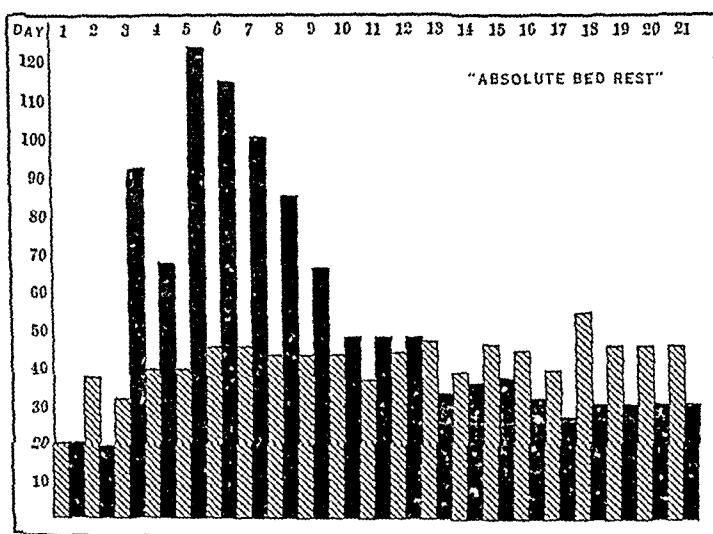
(Chart V); and interestingly in all periods of hospital stay a satisfactory ratio was maintained between output and intake succeeding the primary period of diuresis.

CHART IV.



Digitalis. This drug has occupied an unexcelled position in the treatment of dropsy since the original observations of Withering.¹⁰ His injunctions relative to the physiologic limits of the drug indicate

CHART V.



his ideas as to the importance of its several actions. "Let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels." Interestingly he controlled purging by opium since

digitalis apparently had less diuretic action in the presence of diarrhea. A further point of Withering's practice with regard to the treatment of dropsy is interesting in another relation: "The patients should be enjoined to drink very freely during its operation. I mean, they should drink whatever they prefer, and in as great quantity as their appetite for drink demands. This direction is the more necessary as they are very generally prepossessed with an idea of drying up a dropsy by abstinence from liquids, and fear to add to the disease by indulging their inclination to drink." He outlined the limitations and the usefulness of the drug thus: "It seldom succeeds in men of great natural strength, of tense fiber, of warm skin, of florid complexion, or in those with a tight and cordy pulse. If the belly in ascites be tense, hard, and circumscribed, or the limbs in anasarca solid and resisting, we have but little to hope. On the contrary, if the pulse be feeble or intermitting, the countenance pale, the lips livid, the skin cold, the swollen belly soft and fluctuating, or the anasarcaous limbs readily pitting under the pressure of the finger, we may expect the diuretic effects to follow in a kindly manner."

From a practical standpoint little can be added to Withering's observations, but his conclusions admit of a different explanation for the diuresis on the administration of digitalis in cardiac dropsy. Many clinical investigators (Mackenzie,¹¹ Cushny,¹² Cohn,¹³ Christian¹⁴ and others) have reported diuresis from digitalis only when there is edema. The present viewpoint in this matter is well expressed by Hatcher:¹⁵ "None of the drugs of this group are actively diuretic through any direct action on the kidneys. They induce diuresis solely through an improved circulation. That does not mean either a higher or a lower blood pressure in every case: it means a more effective circulation, one better adapted to the needs of the individual patient. This sometimes means an increase, sometimes a decrease, in pressure." (Chart IX.)

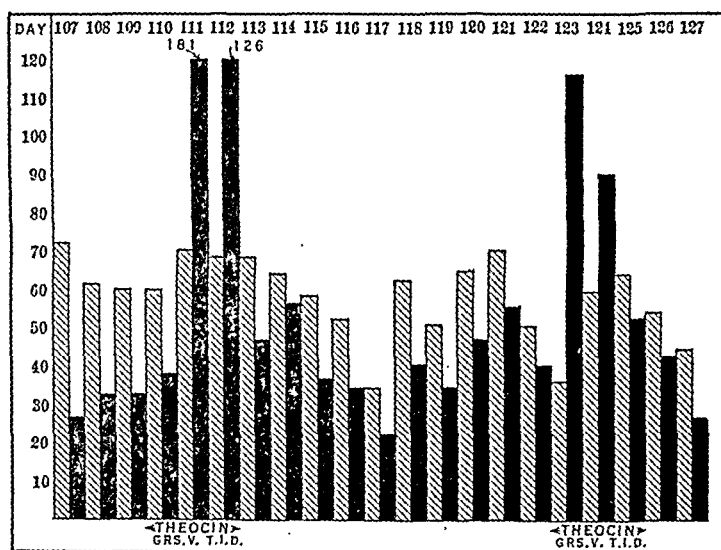
Xanthin Diuretics. Marvin¹⁶ has very ably discussed this important group of diuretics, caffeine, theobromin and theophyllin. His cases of congestive heart failure received the usual digitalis therapy, which was effective in the relief of edema in 36 of the 77 patients treated. Failing to effect diuresis with digitalis, the various xanthin diuretics were exhibited in turn. Theobromin proved more effective than theobromin sodiosalicylate, and theophyllin was the most active of the group.

The experience in the small group of cases under discussion strongly supports Marvin's conclusions; but no distinct contrast in the diuresis effected in the arteriosclerotic hypertensive myocardial cases as compared with the group of the rheumatic background could be deduced. Vertigo, headache, nausea, gastric distress and vomiting limit the wider usefulness of theophyllin. Theocin, the synthetic theophyllin, has repeatedly demonstrated

its diuretic potency after bedrest, dietary control and digitalis have failed to effect improvement.

CASE IV (3866), a white male, aged forty-three years, laboratory technician by occupation, was admitted for the second time in a state of grave cardiac decompensation, on June 15, 1927. The background for this condition was found in a hypertensive myocardial degeneration. Waterlogging was extreme and recurrent. The response to rest in bed, salt poor diet, fluid restriction, digitalis and venesection was erratic. The diuresis on the administration of the xanthin derivatives was prompt and repeated as may be gathered from Chart VI. The most striking incidence of this action occurred on the one hundred and fourth day, when on the exhibition of theocin (grains 10, three times daily) the patient excreted 10,055 cc. of urine with an intake of 2040 cc. The duration of hospitalization rules out rest in bed and dietary responsibility for the occurrence of diuresis.

CHART VI.



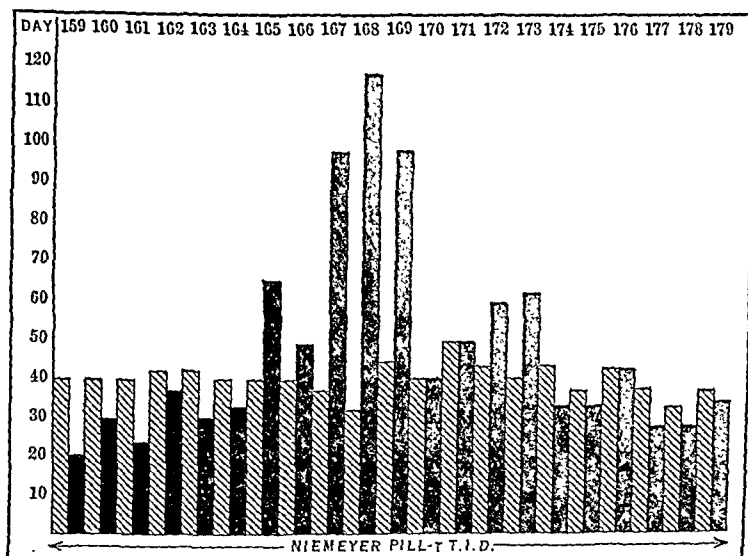
Mercury. This chemical operates as an irritant diuretic, and for this reason the integrity of the kidney should be ascertained before its exhibition. Furthermore, it is necessary that the mercury enter the circulation. For this reason, *Massa hydrargyri* of the Niemeyer pill has been replaced by calomel in our practice. With a compound of this order, it is difficult to evaluate the effective fraction; but if the digitalis alone has been ineffectual in combating the edema, the success of the combination (digitalis, squills and calomel) may be inferred to arise from the mercury. This reasoning is not above criticism, but such is the natural inference. Not infrequently the Niemeyer pill is successful, when digitalis or digitalis and the xanthin diuretics have been unavailing.

CASE V (6528), a white male, aged fifty-five years, had been a cardiac cripple for six years as the result of a rheumatic carditis. From the observa-

tions of this period of decompensation the conclusion of the following sequence of events was derived: rheumatic endocarditis involving the aortic and mitral valves, cardiac hypertrophy with myocardial degeneration, auricular fibrillation and relative tricuspid insufficiency, arteriosclerosis and hypertension.

Response to rest in bed, diet, fluid and salt restriction, paracentesis abdominis, digitalis and the xanthin diuretics was prompt and satisfactory. The accompanying segment of his complete chart (VII) was selected because

CHART VII.

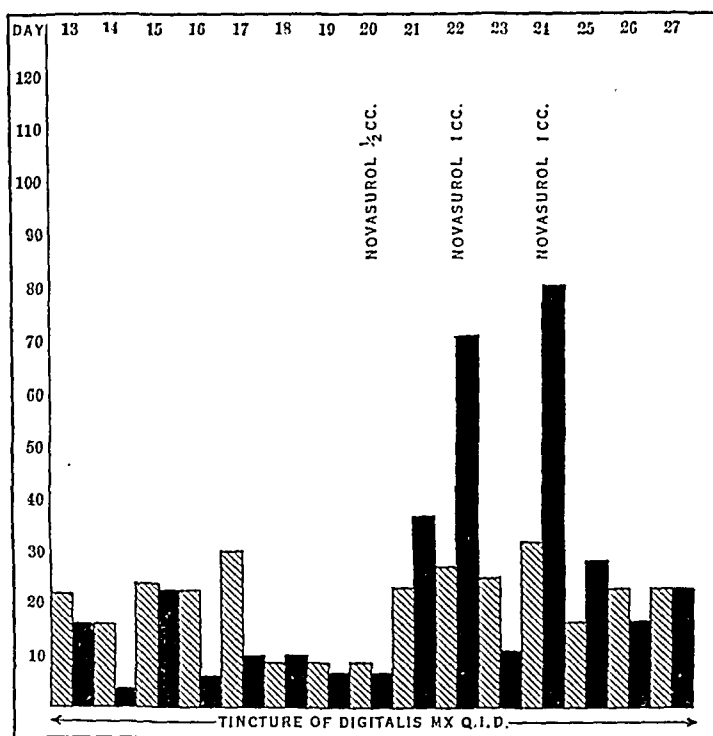


it demonstrates a period of diuresis at an interval of hospitalization (one hundred and fifty-nine days) of sufficient length of time to rule out the factors of rest in bed and diet and apparently dependent upon the administration of the modified Niemeyer's pill.

Of recent origin is novasurol, a mercurial adapted to intramuscular and intravenous use. Keith, Rowntree and others¹⁷ were responsible for its general use in this country in cirrhosis of the liver and nephritis, particularly, while the application of its diuretic action in cardiac edema was advised by Crawford and McIntosh.¹⁸ Their results ranked novasurol as a final court of therapeutic appeal, after digitalis had failed. Of its potency, there can be no reasonable question. Ptyalism, nausea, vomiting, diarrhea, albumin and red blood cells in the urine have been reported from novasurol. Both of 2 cases showing mild evidences of mercury poisoning after its use in the Wisconsin General Hospital had shown a phenolsulphonephthalein output of less than 50 per cent prior to its administration; and since it was the only evidence of renal insufficiency in either case this criterion has been used for the final judgment as to the wisdom of exhibiting novasurol. Case VI is an example of the action of novasurol on a very mild scale.

CASE VI (10303), a negress, aged fifty years, domestic by occupation, presented dyspnea, general anasarca, passive congestion of the lungs and liver, mitral valvulitis, cardiac hypertrophy and dilatation, hydrothorax and ascites. Rheumatic fever at twenty-four years of age had been the etiologic factor in the endocardial lesion, apparently. Arterial hypertension completed the picture. Rest in bed, venesection, theophyllin and digitalis effected some general improvement, but the fluid accumulations and edema persisted. The first sharp positive fluid balance was effected by the intramuscular administration of novasurol (0.5 cc.) on the twentieth day of hospitalization. Apparently in response to each of the three doses of this mercurial drug, diuresis occurred (Chart VIII.)

CHART VIII.



Interesting in the group under study has been the apparent delay in diuresis after novasurol, when the principal seat of the dropsy has been a serous cavity. In such cases a lag of twenty-four to thirty-six hours has been remarked in place of the accustomed prompt diuresis. No experience has been had with the coincident use of ammonium chlorid and novasurol.

The results of the study of the various drugs with relation to diuresis in these cases are enumerated in Table III.

The small numbers involved do not admit of generalization, but at a glance the advantage of theocin over theobromin sodiosalicylate and of novasurol over theocin would seem apparent. Niemeyer's pill obviously holds a relatively high position and is worthy of consideration. In evaluating the utility of digitalis, as with the

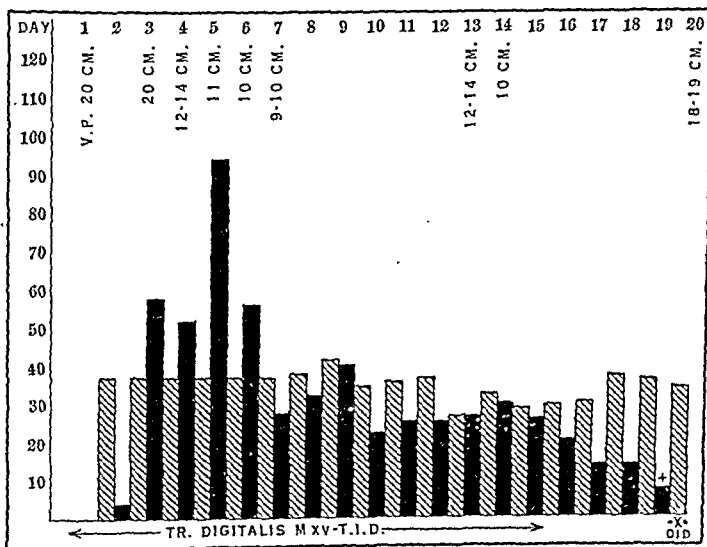
other drugs, no virtue is attributed to the rise in urinary output, apparently almost constant to cardiac decompensated cases with edema on bedrest and dietary control. If this circumstance be taken into consideration, the remarkable effect of digitalis in bringing about diuresis becomes apparent.

TABLE III.—RESPONSE TO DRUGS.

Drugs.	Administration.	Result.		
		+	?	0
Theobromin sodiosalicylate	First	2	3	5
	Repeat	0	1	0
Theocin	First	4	2	4
	Repeat	2	1	1
Novasurol	First	7	1	5
	Repeat	7	0	0
Niemeyer pill	First	5	0	1
	Repeat	0	0	0
Digitalis	Alone	55	5	10
	Combined	10	0	1

Mechanical Factors. The relationship between the venous pressure and the urinary output has been previously mentioned. It can best be demonstrated by an illustrative case.

CHART IX.



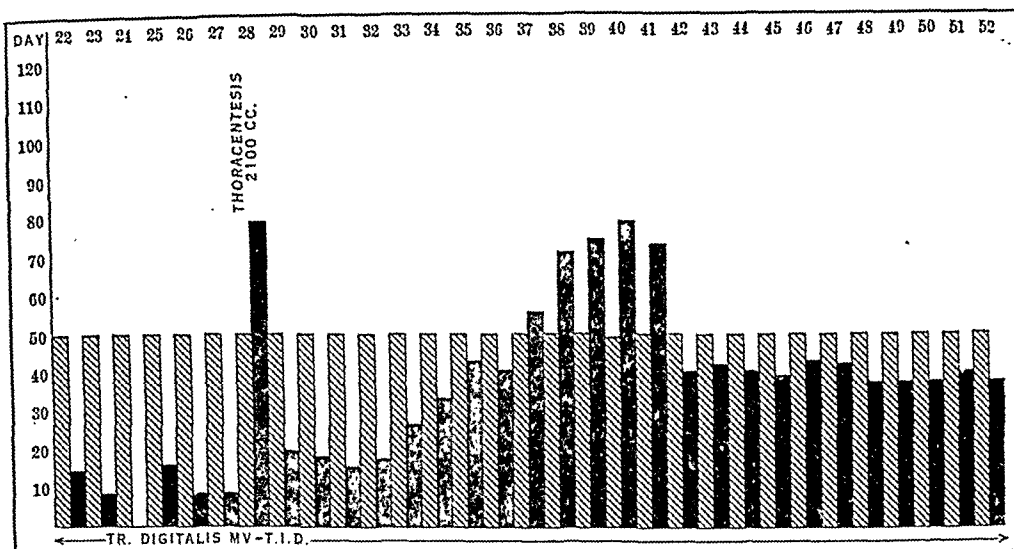
CASE VII (1976), a white female, aged sixty-two years, domestic by occupation, gave a history of scarlet fever and repeated attacks of tonsillitis, prior to tonsillectomy ten years ago. Evidences of cardiac incompetency, orthopnea, cough, precordial pain and abdominal distention, dated back six months. As a background for the decompensation there were determined a double mitral lesion, cardiac hypertrophy and dilatation with relative tricuspid insufficiency, and arteriosclerosis.

A fall in venous pressure was marked by a coincident diuresis (Chart IX). To emphasize the important interrelation of these factors a subsequent

rise in the venous pressure resulted in a sharp fall in the output. The influence of digitalis therapy in this relation may be clearly inferred from the time relationship of its exhibition and withdrawal to the improvement and the recrudescence in circulation incompetency.

Occasionally, striking changes in the water balance result from the removal of fluid accumulations from one or other of the serous cavities. Just how much of this effect is determined by the improvement in the general circulation is impossible to state. In any event Case VIII is an excellent example of the occurrence.

CHART X.



CASE VIII (3754), a white male, aged seventy years and a building inspector by occupation, was readmitted on May 25, 1926, complaining of progressive insomnia and dyspnea. The original findings of arteriosclerosis with myocardial degeneration, right bundle-branch block and cardiac decompensation were confirmed. From a mechanical standpoint, the existence of a bilateral hydrothorax was deemed highly important. Accordingly, the left thorax was aspirated on the eighth day and 1800 cc. of a straw-colored translucent fluid obtained. The subjective and the objective improvement after this procedure were not remarkable. Furthermore, an intolerance to digitalis led to the continuance of inadequate dosage. Singularly a markedly negative water balance pertained and from the time of admission until the second thoracentesis on the twenty-eighth day there occurred only two days of a 60 per cent plus output. The reaccumulation of fluid in the left chest led to the second aspiration and the curve of diuresis thereafter is most striking (Chart X). Concurrent general improvement attended the alteration in the water balance.

Multiple scarifications for the relief of tension in edema of the legs have been attended at times not only by marked loss of fluid by this route with general improvement but also by a subsequent diuresis.

Conclusions. 1. By reason of the circulatory relations of the kidneys, their functional activity is intimately bound up with the integrity of the general circulation. Hence, an unusual prognostic importance is attached to the study of the water balance in cardiac decompensation.

2. The simplicity of the output-intake observations should recommend their routine application to the general practitioner in the group of cases under discussion.

3. The influence of various physical and medicinal factors is discussed with reference to diuresis in decompensation. Calcium chlorid and ammonium chlorid have been used too infrequently to warrant their inclusion in the present relation.

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THE HEREDITARY TYPE OF ANGIONEUROTIC EDEMA.

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QUINCKE's disease, or angioneurotic edema, commands the interest of students of medicine because it belongs in the realm of the unknown and because of the hope that they may discover new and pertinent facts to aid in unveiling the mystery with which it is

surrounded. This disease is of special interest because of its protean symptomatology, the diversity of opinion regarding its etiology, and the fact that it may or may not have familial characteristics.

The familial type of the disease is the least common and because of its rarity we are adding to the literature the reports concerning another afflicted family. The family consists of twenty-four members representing four generations. Six members of this family probably afflicted with the disease have died suddenly: two of undoubted edema of the glottis, two of obscure gastrointestinal colic, one of dropsy and one of heart disease. In this respect the family does not differ from the twenty-one others that have been described in the literature.

Report of Cases. CASE I.—A man, aged thirty-three years, registered at the clinic, March 9, 1923, complaining of cutaneous swelling and bowel trouble. For at least ten years he had been subject to attacks of localized edema of any area of the body, but especially the extremities, neck, lips, scrotum and throat. The attacks occurred about once a month, and he was incapacitated for two or three days. A typical attack was usually ushered in with tingling over a small area. Within a few hours the part became noticeably swollen; this progressed for from six to twelve hours, then gradually subsided for a like period. The swollen area was sharply defined with a definite ridge, probably about 1 cm. deep, which slowly spread "like a rising tide." Pain, itching or color change was not associated. The edema constituted a uniform tense nonpitting swelling. The involvement was usually unilateral, but had been bilateral and symmetric.

Four attacks had occurred, associated with marked edema of the face and neck, in which the patient became panicky, felt as though he was suffocating and breathed, talked and swallowed with difficulty. He felt best when lying down. The entire pharyngeal mucosa became swollen and the uvula was greatly enlarged, and hung down into the lower part of the pharynx.

For many years the patient had suffered periodically from bowel trouble, of which the dominant feature was colic. The distress began in the left iliac quadrant, gradually spreading over the entire abdomen, becoming progressively more severe. After a period of from twelve to fifteen hours he felt faint and weak, usually breaking out in profuse perspiration. On several occasions syncope developed. The abdomen was distended, but there was no flatulence. Usually the bowels did not move even with the aid of drastic cathartics. During the subsidence of an attack he noticed a great deal of borborygmus. He was unable to eat during such an attack; the tongue became heavily coated and the breath foul. These attacks may have been independent of or associated with the cutaneous edema. He usually noticed oliguria during an attack and polyuria afterward. There were no digestive disturbances in the interim and no vomiting during the crisis.

The patient's neuropathic tendencies were shown by excessive nervousness, worry or depression and aërophagia. He could not ascribe a definite cause to his attacks. They seemed sometimes to follow slight trauma and sometimes they occurred after he had partaken of tomatoes, strawberries or lemonade. Such food, however, had been taken repeatedly without the precipitation of an attack. He had never taken antitoxin or serum. He had never suffered from hay fever, asthma, toxic dermatitis or purpura or other hemorrhages.

The general examination was negative, except for the presence of inguinal hernia and rather marked myoidema and dermatographia. While the patient was in the hospital for the repair of the hernia angioneurotic edema, involving the left arm to the elbow and the sole of the left foot, developed. The arm showed increased turgidity and the temperature of the affected area was 98° F. as compared to 94° F. for a corresponding area on the normal arm. The pulse rate was 60. The actual difference in circumferences of the affected and unaffected arms measured in centimeters was as follows: palm, left 24.5 and right 22; third finger, left 8 and right 7; wrist, left 19 and right 18; thumb, left 7 and right 7; forearm, left 27.5 and right 26; arm, left 31 and right 31.

The capillaries were studied and the volume of blood determined by Brown, both during and after the attack. Microscopic observations of the capillary loops during an attack, and three weeks afterward did not show change. The injection of vital red dye did not show increase in permeability nor was there extravasation. The results of determinations of blood volume made during an attack and again three weeks afterward are as follows:

	Weight, kg.	Height, inches.	Hematocrit, per cent.		Total plasma volume for each kilo- gram, cc.	Whole blood volume for each kilo- gram, cc.	Hemo- globin (Palmer), per cent.
			Plasma.	Erythro- cytes.			
During attack . . .	74	68.75	57	43	64	113	133
Three weeks after- ward	70	60	40	57	94	111
Normal	60	40	50	90 to 100	

Skin sensitization tests for beef, tomato, strawberry, potato, lactalbumin, pork, whole wheat, horse serum, whole egg and oats, carried out with a control, were all negative. Tests of the blood showed urea, 22 mg.; urea nitrogen, 10.3 mg., and uric acid, 5 mg., for each 100 cc. A fragility test of the erythrocytes was 0.44 to 0.34 per cent as compared to a control 0.42 to 0.34 per cent. Prothrombin time ranged from ten minutes for 2 drops to fourteen minutes for 8 drops. Coagulation time by the Boggs method was five minutes and by the Lee method nine minutes. Calcium coagulation time was nine minutes and bleeding time two and five-tenths minutes. There were 192,000 platelets. The urine was normal. A complete blood count was normal. The Wassermann test (Kolmer modification) was negative. The basal metabolic rate was -1. Examination of the fundus and a roentgenogram of the colon were negative. Roentgenograms of the teeth showed questionable infection of three.

A recent letter from the patient stated that his general health since the operation for hernia had been good except for the attacks mentioned. He believes these are less severe than they were a few years ago. Months sometimes elapse without attacks, but they may occur as often as every two weeks. There had been only one laryngeal attack in the last five years, but numerous surface swellings and gastrointestinal attacks have occurred (Fig. 1).

Family History. The disease was probably inherited from the father's side of the family. The paternal grandmother and the great grandparents on her side apparently died of old age. The paternal grandfather dropped dead suddenly, presumably from heart disease. Nothing is known of the great grandparents on the paternal grandfather's side of the family. The family has been traced for five years.

The patient's father, now aged sixty-seven, stated that for many years swellings, especially of the hands and scrotum, had occurred, and that for a similar period gastrointestinal attacks had been frequent. He described such attacks as beginning with distress high in the epigastrium, and growing more and more severe as it traveled downward; by the time it had reached the lower part of the abdomen it became severely acute. The pain persisted until the bowels moved, then gradually subsided. He sometimes became quite ill and vomited during the attack. Sometimes certain foods seemed to be the cause and again he seemed unaffected by the same foods.

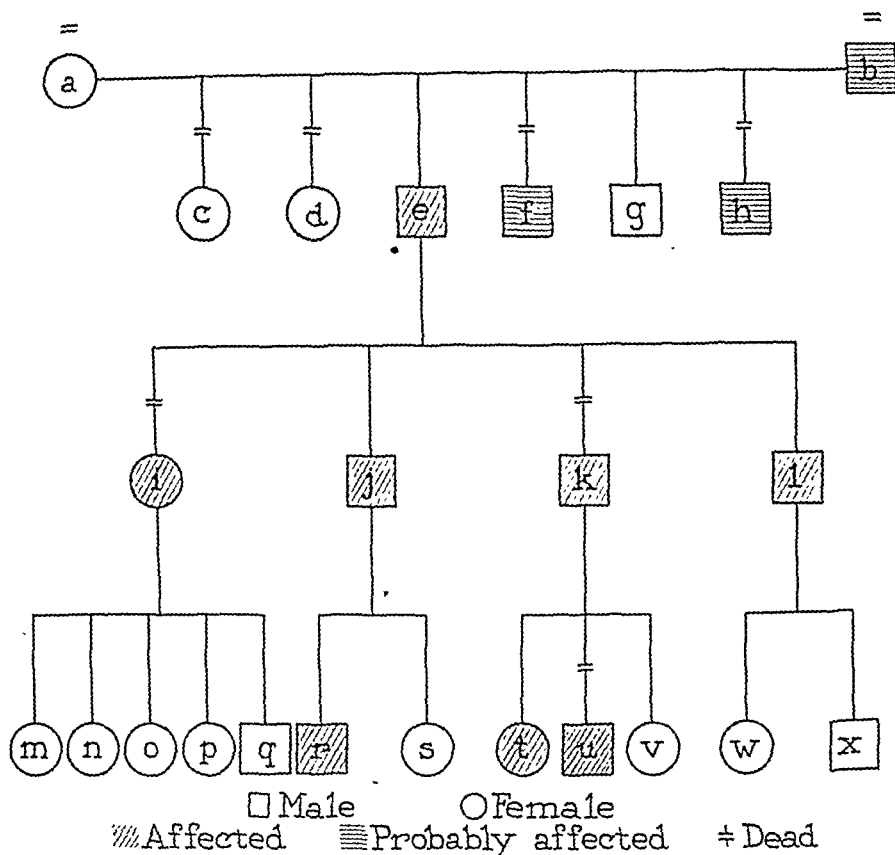


FIG. 1.—(a) Died, aged ninety; (b) sudden death; (c) and (d) causes of death unknown; (e) patient's father aged sixty-seven, cutaneous and gastrointestinal type; (f) sudden death, aged fifty-eight, gastrointestinal colics; (h) sudden death as youth, "dropsy;" (i) died of edema of glottis, aged thirty-five had cutaneous, gastrointestinal and laryngeal type; (j) aged forty-two, gastrointestinal and cutaneous type; (k) died aged twenty-seven, edema of glottis also had cutaneous and laryngeal type; (l) patient aged thirty-seven, cutaneous, gastrointestinal and laryngeal type; (r) aged nine, cutaneous type; (t) aged sixteen, cutaneous and laryngeal type; (u) died aged fourteen, suddenly obscure gastrointestinal colic (g, m, n, o, p, s, v, w, x) living and healthy.

Two aunts had died of unknown cause. One uncle had suffered from gastrointestinal attacks for years and died suddenly at the age of fifty-eight years. One uncle died suddenly of "dropsy" when a young man. One sister, from the age of twenty years, had had repeated attacks of edema of the larynx and died in such an attack at the age of thirty-five years. In her youth repeated attacks of swelling of the hands, feet and neck, and bowel trouble similar to that described by the patient, had occurred. This sister had five children, all living and well. The oldest is only nineteen years of age, however, and the malady may yet develop.

One brother had had repeated acute gastrointestinal attacks of unknown cause since the age of twenty years. At first they occurred every two or three weeks, lasting about two days, but for the last six years only three had occurred each year. During an attack there was severe abdominal pain, bloating, soreness and a feeling of obstruction. Nausea, profuse perspiration, faintness and scotoma were frequent symptoms. During such an attack little if any urine was passed. Cutaneous swellings, usually of the genitalia or arms also occurred. This brother had two children; the oldest, aged nine years, had suffered from swellings of the body and from laryngeal attacks; one of the worst attacks had occurred during chickenpox.

One brother died at the age of twenty-seven years, during his first attack of edema of the larynx. This followed the administration of serum given as a therapeutic measure in the treatment of transient swelling of the surface of the body, that had recurred for many years. This brother had three children, all aged less than sixteen years. The oldest, a girl, had suffered repeatedly from swelling of the surface of the body and attacks of edema of the larynx; in one such attack she almost died. The second oldest child, aged twelve years, died suddenly in March, 1926. The diagnosis was appendicitis; operation was not performed. Abdominal seizures had occurred previously but surface swellings had not been noted.

The following 3 cases of angioneurotic edema or urticaria, although not of the familial type are reported because of the diversity of symptoms and the special studies which were carried out on blood volume and the type of capillaries.

CASE II.—A Greek, aged thirty years, registered at the Mayo Clinic, April 13, 1923. Prior to the onset of urticaria he had been in perfect health, except for occasional attacks of migraine. Early in 1917, within ten minutes after having eaten buckwheat cakes, diffuse, white, itching swellings appeared over the entire body. The face was so bloated that the features were unrecognizable. For half an hour he was so dyspneic; he could scarcely breathe or talk. The abdomen became distended and he vomited; there was no colic. Since then when he is in a room where buckwheat flour is being mixed, if he eats buckwheat cakes or any kind of nuts, or if he is bitten by a mosquito, a severe reaction, characterized by itching wheals over the body, greatly swollen lips, marked dyspnea, profuse nasal secretion, sneezing and blockage of the nose develop immediately. This passes off in from thirty to forty-five minutes. Hay fever, asthma or purpura has not occurred.

The patient was in good physical condition. The systolic blood pressure was 130 and the diastolic 78. The urine and blood were normal. The Wassermann test of blood and spinal fluid and the gold-sol curve were negative. Examination of the nose and throat disclosed septic tonsils and deflection of the nasal septum with obstruction. A roentgenogram of the chest was negative.

Skin-sensitization tests for whole egg, oats, lactalbumin, peanuts and corn, carried out with a control, were all negative. The tests for English walnuts and potatoes were graded 1+, and for buckwheat and whole wheat 3+. A study of the blood volume showed:

	Weight, kg.	Hematocrit, per cent.		Total plasma volume for each kilogram, cc.	Whole blood volume for each kilogram, cc.	Hemo- globin (Palmer), per cent.
		Plasma.	Erythro- cytes.			
Patient	64	54	44	40	87	128
Normal	60	40	50	90 to 100	...

When the patient was last heard from, April 4, 1924, he was having attacks when he ate the food mentioned.

CASE III.—A man, aged fifty-six years, registered at the Mayo Clinic, March 26, 1923, complaining of hives, which had begun twenty years previously with "spells of locking of the stomach." There were severe attacks of constant cramplike pain in the epigastrium lasting three or four hours, leaving him none the worse, except for residual soreness which lasted three or four days. Nausea, vomiting, flatulence or fever had not occurred, and bowel movements were normal. The spells continued for ten years, occurring irregularly, perhaps once a week or skipping months at a time.

The attacks always began suddenly and stopped just as suddenly, so that he "could feel his stomach open up." Cutaneous swellings then occurred at intervals of from two to three days to weeks. Intense pruritus of the palms and the soles developed suddenly, and was followed by generalized eruption or wheals over the body, worse on the face. This would last for half an hour and as suddenly disappear. Two years previously attacks of tingling under the angle of the jaws occurred with a sense of fullness in the neck lasting a few minutes. Then profuse mucous nasal discharge and cough developed. The patient became dyspneic and coughed a good deal; the face became cyanotic and he felt as though he were dying. The attack passed off in about half an hour. Such attacks came irregularly, every few days or with an interval of weeks. The patient ate heavily, and believed that at times acid foods and too much water precipitated attacks. He also attributed the attacks to apples, cherries, onions, peaches and whisky. He was not susceptible to cold and had never had asthma or hay fever.

General examination disclosed obesity, pulmonary emphysema, thyroid enlargement and cardiac hypertrophy, with evidence of myocardial degeneration and beginning decompensation. The systolic blood pressure on two occasions was 160 and 184 and diastolic 100 and 104.

A complete blood count, examination of urine, blood Wassermann test, gastric analysis and gastric roentgenograms were reported negative. A roentgenogram of the chest showed cardiac enlargement (graded 3), with congestion at both bases. An electrocardiogram gave a rate of 90, notched *P* wave in Leads I and II, left ventricular preponderance and inverted *T* wave in Lead I. A skin-sensitization test, carried out with a control, was reported as negative to grapefruit, whole egg, tomato, lactalbumin, beef, whole wheat, pork, casein, corn, rice, oats and potato. The capillaries were normal. A study of blood volume showed:

Weight, kg.	Hematocrit, per cent.		Total plasma, volume, for each kilogram, cc.	Whole blood volume, for each kilogram, cc.	Hemoglobin (Palmer), per cent.
	Plasma.	Erythro- cytes.			
103	53	47	38	71	129

The patient, who is now sixty-two years of age, states that he is working every day, but continues to have the attacks, although less often than at the time of his examination.

CASE IV.—A man, aged thirty-four years, registered at the Clinic, August 22, 1923. In the spring of 1919 he had noted for the first time several isolated swollen areas on his scalp which soon disappeared. He was free from them until the fall of 1921, when several similar areas appeared on his

scalp during the course of the evening and were gone by the next morning. From this time on every two or three days, usually about 8 P.M., the feet, face, eyelids, hands, tongue, lips, buttocks or genitals became swollen, but the swelling had always disappeared by morning. Such lesions were sometimes single and sometimes multiple. They seemed particularly to follow slight trauma, such as swellings of the hands after he had driven a long distance, or of the feet after walking, or buttocks after he had been sitting for a long time. Twice during this period he had had laryngeal attacks with severe dyspnea and cyanosis. There was no gastrointestinal colic.

The general examination was negative. The systolic blood pressure was 130 and the diastolic 80. A complete blood count, analysis of urine, Wassermann test on the blood, roentgenogram of the chest, examination of the fundus and renal functional tests were all reported negative. The platelets numbered 276,000. Coagulation time (Lee method) was five minutes. The prothrombin time varied from thirteen minutes for 2 drops to twenty-five minutes for 8 drops. W. W. Duke* had made a thorough study for allergy and had reported that all tests were negative.

Definition. The term angioneurotic edema implies a condition characterized by acute massive ephemeral swellings of the skin, of various mucous membranes, or of the viscera; a swelling which recedes without leaving a residue. There is a strong tendency to recurrence, particularly in a previously involved area, and in certain cases with extraordinary precision of time. The duration of a single attack varies from hours to one or two days. The condition is chronic, extending over a period of many years apparently without ill effects; in fact, persons affected are usually free of organic disease.

History. Angioneurotic edema as such was first described by Strübing in 1885. Three years previously Quincke had reported the same syndrome under title of acute circumscribed edema. In his description he included not only the recurring edema, involving the skin and subcutaneous tissue, but also the recurring edema of the pharynx, larynx and gastrointestinal tract, as well as the intermittent serous effusions of joints. As far back as 1827 this condition was mentioned in the literature although not as an entity. In 1874 Cuntz reported 4 cases of recurring edema recognized as of angioneurotic origin. Henoch in the same year reported 4 cases of his own and 3 which he had noted in the literature of an unusual form of purpura of nervous origin which he classified as an entity characterized by recurring attacks of purpura, cutaneous edema, gastrointestinal crises and melena. Since Quincke's time various manifestations of this strange malady have been reported under many titles. Cassirer in 1901 reviewed 160 cases from the literature under title of acute circumscribed edema.

Literature. Angioneurotic edema and urticaria were regarded as one and the same prior to the time of Quincke: Oppenheimer still maintains their identity. Crocker regards angioneurotic edema as

* Personal communication.

giant urticaria. Stelwagon and Oppenheim distinguish the two conditions, but recognize their similarity. Kohn believes that urticaria involves the corium while angioneurotic edema involves the subcutaneous tissues. Halsted and Packard include angioneurotic edema, urticaria, asthma and hay fever in one group. Packard reported 36 cases of the occurrence of asthma and urticaria in the same or alternating attacks. Osler, in his third contribution on the subject, pointed out the relationship existent in simple erythema, erythema exudativum, erythema nodosum, herpes iris, certain of the purpuras (including Henoch's purpura) urticaria and angioneurotic edema. He concluded that they belong to one family in that they occur under similar conditions, that frequently the lesions may be substituted one for the other at different times in the same patient, that they tend to recur for many years, and that they cause identical visceral manifestations. Yarian, Chittenden, and Schlesinger concur in Osler's view and report cases in which such complications exist. Joseph and Cassirer reported the occurrence of hemoglobinuria associated with each recurring attack of angioneurotic edema. Packard reported a case of hematuria relieved by outbreaks of urticaria, Holmes one of acute local edema complicated by salivation and purpura, Küssner one of apparently causeless hemorrhages from mucous membranes simultaneously with edema, and Chittenden one of urticaria associated with gastrointestinal attacks of hematemesis or melena. Stokes has called attention to the relationship of erythema nodosum purpura and tuberculosis. Rosenow reported the relationship of erythema nodosum to nontuberculous infections. One of us (Lemon) reported the existence of eczema, adenoids and asthma in the same patient, and similar conditions singly or combined in two other children of the same family; one child of the family was not affected.

Etiology. The causes assigned to angioneurotic edema are almost as diverse as are the titles. It has been fairly well established that thermal changes bear a direct relationship, but whether as a primary or a precipitating cause has not been determined. Particular attention has been directed to its relationship to cold. Starr, Oppenheim, Widowitz, Wills and Cooper, Schlesinger, Cassirer and Morse have cited cases bearing out this view. Kohn, on the other hand, cited a case in which an attack was precipitated every time the patient placed her hands in hot water. Collins stated that attacks are more frequent in the summer and winter than in the spring and fall, due to the variation of surface temperature during and following exertion.

Anaphylaxis as an etiologic factor has frequently been observed. Nifong, Morse, Halsted and others have called attention to the relationship of the administration of diphtheria antitoxin to the occurrence of angioneurotic edema and urticaria. Lederman reported a case in which an attack developed as a result of contact

with a jelly-fish. Crowder and Crowder believe a streptococcic infection may result in an anaphylactic reaction. Halsted believes that toxin and autotoxin, probably of gastrointestinal origin, is a possible cause. Osler cited the relationship of certain foods, hydatids and shellfish to attacks in some cases. Infections have been considered as the causative factor. Matas quoted a case resulting from malarial infection in which cure was effected by quinin. Osler also showed the relationship of malaria and cholecystitis to certain cases. Oppenheimer and Joseph reported cases showing a direct relationship to the ingestion of alcohol. Miller and Pepper, in a study of the chemical condition of the blood, found retention of chlorids and nitrogen preceding and during an attack.

TABLE I.—TABULATION OF CASES FROM LITERATURE.

	Genera- tions.	Members.	Members affected.	Deaths.	Remarks.
Osler	6	42	24	2	
Crowder and Crowder	5	64	28	15	
Ricochon	4	..	9	3	
Schlesinger	4	15	5	..	
Ensor	5	80	33	12	
Dinkelacker	2	4	3	..	Third member reported by Valentin.
Strübing	2	4	3	..	Father, son, daughter.
Falcone	3	..	2	..	Grandfather and child.
Krieger	2	..	2	..	Mother and son.
Fritz	3	9	8	5	Deaths from edema of the glottis.
Roy	2	..	2	..	Mother and daughter.
Yarian	2	15	10	2	One died of edema of the glottis.
Griffith	2	..	2	2	Father and patient died of edema of glottis.
Harbitz	3	..	6	..	
Morris	2	..	3	1	Death from edema of the glottis.
Halsted	3	..	7	..	
Halsted	2	..	4	..	
Halsted	2	..	3	..	
Smith	2	..	2	..	Mother and daughter.
Mendel	4	12	9	6	Deaths from edema of the glottis.
d'Appert and Delille	3	..	5	..	
Dunlap and Lemon	4	23	11	6	Two died of edema of the glottis.

The relationship of angioneurotic edema to nervous disorders, either organic or functional has long been noted. It has been found in association with such nervous disorders as chorea, sciatica, hysteria, migraine, myasthenia gravis, epilepsy, cord tumor, neurasthenia and tabes. Simon reported a case associated with epilepsy. Börner, Joseph, Schlesinger and Cassirer have cited instances of its occurrence in association with exophthalmic goiter. We have frequently noted the occurrence of urticaria in cases of exophthalmic goiter and its alleviation by thyroidectomy. Collins does not believe that the edema associated with organic nervous disorders is the same as that associated with angioneurotic edema. He rather favors a neuropathic cause for the latter. Oppenheim, Quincke, Schlesinger, Widowitz, Cassirer, Bauke, Wills and Cooper, Kohn and Hallock state that it usually occurs in a neuropathic person, or in

a member of a neuropathic family. The relationship of psychic disturbances and especially of emotional instability has been emphasized by Strübing, Cassirer, Schlesinger, Ensor, Packard, Oppenheimer and Crowder and Crowder. The relationship of menstruation and the climacteric to its occurrence has been stated by Börner and Schlesinger. Börner reported a patient having attacks definitely occurring during menstruation and relieved by the onset of the climacteric. Quincke, Strübing and Collins believe that it is a form of vasomotor neurosis. Crowder and Crowder agree with the latter view, but believe that it is dependent on a capillary irritant. The latter, according to Crowder and Crowder, causes either increased secretion of lymph or causes the walls of the vessels to become more permeable, allowing increased transudation. It is Crocker's belief that the whole process is a vasomotor disturbance with spasm of the wall of the vessel followed by paralytic dilatation and stasis or retardation of the circulation in the papillary layer of the skin.

Trauma, even though slight, such as irritation to the genitalia in bicycling may be an etiologic factor. Halsted noted edema of buccal and laryngeal mucous membranes following the use of throat sprays and of applications of zinc chlorid. Three of Crowder's patients died of edema of the larynx after extraction of teeth. Briggs reported 4 cases of fulminating pelvic edema resulting from a nidus of tubal inflammation.

Etiologic Influence of Heredity. It has been recognized since Quincke's observations that in certain of these cases there is a distinct hereditary tendency. It was not until Osler's report, however, that general attention was attracted to the hereditary tendency. Crowder and Crowder believe that direct descent of the tendency is so constant as to suggest inheritance in the strict sense of a trait transmitted as a dominant characteristic under the Mendelian law. Ensor stated that members of an affected family who escape are less likely to transmit the disease than are those affected. Crowder and Crowder did not observe an instance of it in a descendant of an unaffected parent and only twice did all the children of an affected parent escape. The line of inheritance was always direct, not skipping and reappearing. In only 1 instance did Ensor find the offspring of an unaffected parent affected by the disease and in this case there were 7 other children free from the disease. In the family reported by Osler there was 1 unaffected parent who had 3 children all affected, but in the remainder of the family the transmission was always direct. Also, in the families reported by Schlesinger and Ricochon there was no instance of skipping and reappearing. In the family discussed here the transmission was direct through four generations.

The question has been raised repeatedly as to whether inheritance is through the paternal or the maternal side of the family. Fairbanks believes that it is transmitted only through the maternal line

in the acute form. Yarian's cases show preponderant transmission through the maternal side. Cassirer records an instance in which inheritance was entirely through the male. The cases of Quinke, Dinkelacker, Valentin and Strübing were transmitted from father to son. The families reported by Osler and Ensor showed repeated transmission through the male. The families reported by Ensor showed inheritance through the male line in 6 instances for four generations and in 2 instances for five generations. The reports of Osler, Schlesinger, Crowder and Crowder, Ricochon and our case each showed 1 instance of transmission through the male for four generations. Crowder and Crowder also reported an instance of transmission through the female for as many as three generations.

According to Fairbanks, the mortality in the hereditary cases is about 16 per cent, and in the remaining 84 per cent about 6 per cent of patients are in imminent danger during some attack. The cause of death was edema of the glottis in most cases, and usually in adult life. Osler reported 7 deaths in 29 cases (24.1 per cent), but included erythemas, purpuras, and so forth. Ensor reported 12 deaths from edema of the glottis in 35 cases (35 per cent), Crowder and Crowder 15 deaths in 28 cases (51.5 per cent), Yarian 3 deaths in 9 cases (33 per cent), and Fritz 5 deaths in 8 cases from edema of the glottis. Griffith reported 2 cases and Morris 1 from edema of the glottis. McDowell reported an incidence of 30 deaths (37 per cent) among 110 familial cases reviewed by him. In the family reported here there have been 6 deaths, 2 of which were from edema of the glottis. Four deaths were sudden and occurred in questionably affected members of the family (tabulation.)

Symptoms and Course of Disease. Ensor has divided the cases into four clinical groups: (1) in which subcutaneous tissue alone is involved; (2) in which the mucosa of the respiratory and intestinal systems are primarily involved; (3) in which a combined form of edema begins in the face and spreads to the mucosa of the pharynx and larynx, and (4) in which intestinal colic exists without external signs of edema. According to Ensor, Groups 1 and 4 constitute the most common type and are the least dangerous.

Group 1. The cases in this group are the most common. The lesion is typically a large, pale, cool swelling not accompanied by itching, developing rapidly, persisting indefinitely, then subsiding without leaving evidence of its existence. It does not pit except perhaps during recession. The lesions vary greatly in size in various attacks and in different persons. The onset is usually preceded by a short period of intense itching.

Groups 2 and 3. This type of angioneurotic edema is much more common than is generally believed. As stated by Ensor, it may start in the larynx itself or it may spread to the larynx from the face or buccal cavity. The former is far more serious and accounts for most of the deaths in this group. The onset is sudden with

intense dyspnea, and suffocation and death soon ensue unless relieved within a few minutes. Griffith viewed the involved areas several times with a laryngeal mirror. The lesions appeared to be rounded, pale, jellylike, tense masses obscuring the cords. Both Morris and Griffith reported on the laryngeal lesion of a patient who died during an attack of edema of the glottis. The mucous membrane was very edematous, the edema extending down into the deeper connective tissue and muscle; even the tissues over the true cords were markedly affected.

The edema at the same time or independently may involve the nasal mucosa, the sinuses, pharynx, tongue, bronchial mucosa and lungs, accounting for the relationship noticed by Halsted and Packard in cases of angioneurotic edema, urticaria, asthma and hay fever. Ensor reported an instance of acute pulmonary edema. Bloodgood has reported on edema of the sinuses.

Group 4. Gastrointestinal attacks are second only in frequency to surface swellings. They may accompany, alternate with, or precede for many years the cutaneous manifestations. Bogart quotes Osler saying that gastrointestinal attacks occur in 34 per cent of all cases. In Osler's own series of cases 25 of 29 patients suffered from gastrointestinal symptoms. He believed that they did not cause death.

Morris reported noninflammatory edema of a piece of gastric mucosa recovered by lavage during an attack. Bogart reported a case in which he found blood-stained fluid in the peritoneal cavity on exploration, as is found in ileus, with edema of the ileum and jejunum obliterating the lumen of the bowel.

Bogart stated that such crises usually occur in men aged thirty to forty-five years. Colic is the predominant symptom and for years may be the sole manifestation, as in Cases 17 and 27 of Osler's series. The pain is sudden at the onset and severe. Bogart stated that the pain is in the midabdomen, and more or less continuous with paroxysms of greater severity. The patient may appear very ill and on the verge of collapse. There is little if any fever. The abdominal walls are tense, but not rigid, and there is no tenderness. Nausea and severe repeated vomiting are usually associated. The abdomen is distended and the bowels cannot be moved. Occasionally, however, diarrhea, meteorism and melena occur.

Bogart and Osler call attention to the similarity of these cases to those of gall stone or renal colic, intestinal obstruction from intussusception, perforated gastric or duodenal ulcer, appendicitis, hydro-nephrosis, tabetic crises and abdominal migraine. Osler reported 3 cases from the literature and 1 of his own of colic and melena leading to a false diagnosis of intussusception. In cases of children with colic he emphasized the necessity of taking a careful history of previous attacks of colic, of lesions of the skin or arthritis and of looking for purpura, erythema or angioneurotic edema.

Other organs and tissues have been less often involved. Osler reported endocarditis as a rare complication, usually in cases with intense arthritic purpura. He noted 14 cases of acute nephritis in which 5 patients died of uremia. He did not observe the condition in an uncomplicated case of angioneurotic edema. Oliguria was noted by Quinke and Schlesinger as well as ourselves. Schlesinger states that we cannot be sure whether the oliguria is due to edema of the kidneys or is on a circulatory basis due to vasomotor instability. Osler also reported arthritis or arthritic pain in 17 cases. Crowder and Crowder reported enlargement of the uterus in a girl aged eighteen years; the uterus increased to about the size of a "twenty-pound cannon ball" in thirty minutes. Talley noted involvement of the salivary glands and Küssner and Quinke noted ascites.

Oppenheim states that it is uncertain whether angioneurotic edema can cause brain symptoms. He has seen apoplectic attacks occur in a chronic variety of this malady which he felt was possibly of vasomotor origin. In Osler's Case 15 attacks of aphasia and hemiplegia developed, associated with the lesions of the skin.

Summary. The voluminous literature on angioneurotic edema has been briefly reviewed and the disease discussed in its relationship to heredity, etiology, and symptoms. Reports of cases of families described in the literature, have been tabulated. One family is added to those already described. It has not been possible to add much to the understanding of this strange malady.

In this report we have also included 3 cases that did not exhibit familial characteristics. They were added, however, because of the bizarre symptoms and because the studies of the capillary loops and blood volume might throw some light on the mechanism of the production of the edema. The same studies were made on the representative of the familial group, but they did not disclose variations either from those of normal persons or from those on cases without familial tendency.

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IPSOLATERAL EDEMA AND CONTRALATERAL JAUNDICE ASSOCIATED WITH HEMIPLEGIA AND CARDIAC DECOMPENSATION.

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BIZARRE distribution of edema and jaundice is a phenomenon of more than passing interest to the theory of permeability. But few clinical examples, however, have been reported in the literature. It is for this reason that the following cases are presented and discussed from the point of view of their bearing on this important mechanism.

Case Reports. CASE I.—Barney K. (No. 67864) was first seen at the age of ten years, suffering from chorea and mitral insufficiency. Twelve years later he developed a sudden right-sided hemiplegia presumably as the result of dislodgement of a clot from the auricular appendage. At this time his clinical picture was that of a classical case of mitral stenosis and insufficiency, auricular fibrillation and cardiac hypertrophy. About four months were required for convalescence from the hemiplegia. Three

months after this he became decompensated and had bronchopneumonia, but with rest in bed and digitalis his recovery was satisfactory. It should be noted that the liver was felt 3 cm. below the costal margin, whereas there was no peripheral edema. One month later however, he again became decompensated and again using the same régime recovered fair health. There was little of unusual note during these periods.

However, six months later he entered the hospital complaining of pain and swelling in his right hand, arm and leg. His heart was fibrillating and markedly insufficient, many râles were heard in the bases of his lungs and the liver was enlarged 6 cm. below the costal margin. The peculiar feature presenting itself was that in spite of some atrophy of the two right extremities, resulting from the old hemiplegia which had been previously noted, these limbs were very edematous. To our surprise no edema was found in the *left* leg, arm or over the sacrum. On the right side the deep reflexes were all increased over the left, but no positive Babinski or Oppenheim sign nor ankle clonus was found on either side.

The blood pressure was 118 systolic and 80 diastolic, and did not vary greatly throughout his course. After a few days in bed he became slowly jaundiced. The jaundice appeared only on the left side, the edematous parts of the residual hemiplegic side remaining clear. He became progressively more decompensated. Cyanosis appeared but much more prominently in the nails and the lobe of the ear on the edematous right side. As decompensation advanced, bilateral peripheral edema appeared. The patient died shortly thereafter.

On his last admission, the red blood cells numbered 4,200,000 with 87 per cent hemoglobin (corrected to oxygen standard); white blood cells, 15,000, with 80 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes and 3 per cent endotheliocytes. The stool showed no bile; urine bile + + + +; blood urea, 0.26 gm. per liter. Icteric index = 50. Van den Bergh test gave a direct immediate reaction and the indirect = 9.4 units bilirubin (4.7 mg.) per 100 cc. of serum. Electrocardiographic records and Roentgen ray confirmed the diagnosis of rheumatic endocarditis.

Necropsy showed extreme calcification and distortion of the mitral valve. Many thrombi in the auricular appendages, infarcts of the lung and spleen, rheumatic aortitis, rheumatic auriculitis, and other changes characteristic of rheumatic heart disease were present. A terminal bronchopneumonia was also demonstrated. Cardiac cirrhosis was present to a marked degree in the liver, for example, reticulum-cell condensation as the result of long-continued chronic passive congestion.

CASE II.—No. 71123 (female, aged thirty-seven years). Three years before admission to the hospital, this patient had a curettement, following which she suddenly became paralyzed in the right hand and arm. A few months after this she developed acute polyarticular rheumatism associated with endocarditis. Six months later she had the physical signs of typical rheumatic heart disease and her heart was fibrillating. Shortly thereafter began a series of convulsive seizures and transient paralyses, which strongly suggested multiple cerebral emboli. Three weeks before admission to the hospital, she became rapidly decompensated. Her legs and abdominal wall were massively edematous. The arm in which the paralysis had occurred became tense with edema even up to the neck but the other arm (left) remained free. Shortly before death she became slightly jaundiced but none appeared in the edematous arm and legs whereas the rest of the body showed an ictteroid tint. The serum bilirubin was 3.75 mg. per 100 cc. serum; the blood urea, 1.04 gm. per liter.

Discussion. There is not at present any unqualified proof of the direct control of permeability by the nervous system. There are

many experiments and examples which suggest this however. If, for instance, the right cervical sympathetic system is removed from an animal, and fluorescein injected into the peritoneum, the dye may subsequently be seen in the right vitreous but none in the vitreous of the left eye.¹ Various secretions, such as the saliva, seem to be liberated as the result of permeability changes mediated by a nervous impulse.

Hemiplegia certainly produces vasomotor paralysis or instability. This is shown by the trophic changes in the right limbs and the ipsilateral cyanosis observed in our case.

A paralytic dilatation of the capillaries, resulting from the lack of tonic influence of the vasomotor system, may result in active transudation of fluid. From the work of Landis,² we may assume that the dilatation *per se* is not responsible for this occurrence, but rather must refer it to a change in cell permeability. A further factor resulting from vasomotor paralysis is arterial hyperemia. Increased filtration pressure is thus produced which in turn may facilitate fluid transfer from vessel to tissue. At present, there are not sufficient data to prove that there is a change in the osmotic pressure of the blood in these cases of regional edema.

Local anoxemia as a result of: (1) Deficient oxygenization of the blood in the lungs, and (2) increased oxygen consumption resulting from the stagnation of the blood in the capillaries may well be one of the causative agents initiating these permeability changes.

It is worthy of note that this patient had visceral manifestations of edema before any peripheral signs appeared and that when the peripheral signs did appear they were localized to one side. This raises the question of where edema first manifests itself in cardiac decompensation. If cardiac edemas are associated with capillary anoxemia we should anticipate that edema would first appear in the viscera and the peripheral signs follow later.

Meakins³ has recorded an interesting series of cases of jaundice in circulatory failure. He points out that two types of jaundice may occur in this condition: (1) Those which are analogous to hemolytic jaundice in which there is either an excess of the precursor of the bile pigments produced in the spleen or an inability on the part of the liver to transform the precursors into bile pigments or (2) the obstructive type of jaundice where, although the bile pigments are formed from their precursors and secreted into the bile capillaries, they are prevented from passing into the large ducts.

In the first case, a positive indirect van den Bergh test would be expected, whereas in the latter a direct as well as indirect would be obtained. It is to the obstructive type that our patients belong.

It is difficult to understand why bile pigments are unable to enter edematous tissue. The close association with the metallic salts of the glycocholates and taurocholates would lead one to anticipate a ready entrance through the cell membrane, when it is remembered

that these salts are very highly surface active. There is, however, no proof that the pigments are necessarily associated in the blood serum with these salts. Furthermore, we do not know whether the bile salts enter the edema fluid. If it could be shown that such an association occurred, it would be even more difficult to explain why they did not render the cells sufficiently permeable to allow the entrance of the pigment.

Ample data have been published to prove that the size of the molecule need not necessarily influence the selective penetration of a substance. Therefore we cannot assume that these pigments do not enter the edematous cells for reason of size alone.

We can only suggest that the turgor of the cells, due to the edema, may in some way hinder the entrance of the pigment. There are so many factors that need study that at present any adequate explanation of the lack of penetration of bile pigments into edematous cells seems little more than speculation.

Summary. Two cases of ipsilateral edema and contralateral jaundice on the basis of cardiac decompensation following hemiplegia are presented and the relation of this phenomenon to cellular permeability discussed.

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REVIEWS.

OSLER'S MODERN MEDICINE. VOL. VI. Re-edited by THOMAS McCRAE, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia. Third edition. Pp. 964; 65 illustrations and 3 colored plates. Philadelphia: Lea & Febiger, 1928. Price, \$9.00.

OSLER'S MODERN MEDICINE. GENERAL INDEX. Pp. 126. Price, \$1.00.

PART I deals with the Diseases of the Nervous System, including an introductory chapter (L. F. Barker); chapters on Diseases of the Motor System (W. G. Spiller); the Combined System Diseases of the Cord (C. K. Russel); Scleroses of the Brain, Diseases of the Meninges (E. Bramwell); Tropical Diagnosis of Diseases of the Brain, Aphasia (J. Collins); Intracranial Tumors, Hydrocephalus (H. Cushing); Acute Encephalitis and Brain Abscess, Epidemic Encephalitis (J. R. Hunt); Diseases of the Cerebral Bloodvessels (H. M. Thomas, Jr.); Diseases of the Cerebral Nerves (E. W. Taylor); Diseases of the Peripheral Nerves (G. M. Holmes); Diffuse and Focal Diseases of the Spinal Cord (E. F. Buzzard and C. P. Symonds); Epilepsy (L. P. Clark); Neurasthenia, the Traumatic Neuroses and Psychoses (C. W. Burr); Hysteria, Migraine, Neuralgia, Professional Spasms, Occupation Neuroses, Tetany (S. E. Jelliffe); Paralysis Agitans, Chorea, Choreiform Affections, Infantile Convulsions, Myasthenia Gravis, Paramyoclonus Multiplex, Periodic Paralysis, Astasia-Atasia, Adiposis Dolorosa (D. J. McCarthy); Syphilitic Diseases of the Nervous System, Amaurotic Family Idiocy (B. Sachs). Part II is composed of a chapter on the Diseases and Abnormalities of the Mind (E. A. Strecker). A perusal of the list of contributors will in itself suffice to convince the reader of the uniform excellence of the whole volume. A thorough and complete index in a separate handy volume is a welcome new departure.

R. K.

ACUTE INFECTIOUS DISEASES. By JAY FRANK SCHAMBERG, A.B., M.D., and JOHN A. KOLMER, M.Sc., M.D., DR.PH., D.Sc., LL.D. Second edition. Pp. 888; 188 illustrations. Philadelphia: Lea & Febiger, 1928. Price, \$10.00.

THIS excellent account of the acute infectious diseases by two well-known authorities may be highly praised with safety. This new edition has not only been extensively revised, but a number of new

chapters on diseases not formerly included have been added. The clinical phases of the chapters on vaccinia, smallpox, chickenpox, scarlet fever, measles, rubella and typhus fever have been in considerable part retained. The chapter on diphtheria has been rewritten and new chapters on the prevention of diphtheria, Vincent's angina, serum anaphylaxis, erysipelas, mumps, whooping cough, cerebrospinal meningitis, the "fourth disease" and erythema infectiosum have been added.

E. K.

LABORATORY MANUAL OF THE MASSACHUSETTS GENERAL HOSPITAL. By ROY R. WHEELER, M.D., and F. T. HUNTER, M.D. Second edition. Pp. 101. Philadelphia: Lea & Febiger, 1928. Price, \$1.75.

THE second edition has been brought up to date and offers in compact form a most useful compendium of laboratory methods.

O. P.

GOITER PREVENTION AND THYROID PROTECTION. By ISRAEL BRAM, M.D. Pp. 327; 13 illustrations. Philadelphia: F. A. Davis Company, 1928. Price, \$3.50.

THIS volume is intended primarily for the laity, and represents the author's views on the physiology and pathology of the thyroid gland as well as the treatment of simple and toxic goiter. There is an appendix dealing briefly with the other glands of internal secretion. About one-fifth of the book is devoted to an exposition of the author's views on the etiology and treatment of exophthalmic goiter; his unreserved condemnation of surgical treatment in this condition represents a minority opinion. The style is not classic and there is frequent repetition of ideas. The volume does not represent a notable addition to the literature on its subject.

E. R.

CHEMOTHERAPEUTIC RESEARCHES ON CANCER. WITH ESPECIAL REFERENCE TO THE LEAD AND SULPHUR GROUPS. By A. T. TODD, M.B. (EDIN.), M.R.C.P. (LOND.), Hon. Assistant Physician, Bristol Royal Infirmary; Lecturer in Pathology, Bristol University. Pp. 127; 11 illustrations. Bristol: J. W. Arrow-smith, Ltd., 1928. Price, 2 s., 6 d.

SEVERAL interesting chemical and clinical studies of the combined effects of colloidal lead and selenium in the treatment of

inoperable cases of cancer, based on the possibility that the combination of the two substances might work more efficiently than either singly and that the analgesic effects of selenium might mitigate the painful effects both of advanced cancer and of the lead treatment. Though the 12 cases abstracted in the first article are meager and entirely inadequate, the improvement noted—always a dangerous criterion for evaluation—appears to the author to justify his expectations.

In a later series of 44 cases, pain was relieved in about one-half and growth retarded in 24 out of 40 cases. E. K.

CLINICAL MEDICINE. By OSCAR W. BETHEA, M.D., PH.G., F.C.S., F.A.C.P., Professor of Therapeutics, Tulane Graduate School of Medicine; Professor of Clinical Therapeutics, Tulane School of Medicine; Chief of Medicine, The Baptist Hospital, New Orleans; Senior Visiting Physician, Charity Hospital of Louisiana; Medical Director of the Standard Oil Company of Louisiana. Pp. 700. Philadelphia: W. B. Saunders Company, 1928. Price, \$7.50.

THIS book, being the outgrowth of lectures of a professor of clinical therapeutics, has its emphasis entirely on clinical medicine and therapeutics. Its appeal is therefore somewhat limited. Sections of it might be rewritten with profit, for though there is considerable repetition throughout, the treatment of certain topics is inadequate, notably that of purpura. There is no mention, either, of Small's treatment for rheumatic fever, and only a glancing reference to Minot's treatment of primary anemia. One might take exception, too, to certain statements, as that which describes "benzol as the outstanding medical agent in general use" for leukemias. Within the bounds of its limitations, however, the volume is helpful. There is a wealth of detail on bedside diagnosis and treatment. K. A.

THE DUODENUM. By PIERRE DUVAL, JEAN CHARLES ROUX and HENRI BÉCLÈRE, Surgical Clinic, Faculty of Medicine, Paris. Translated by E. P. Quain, M.D. Pp. 212; 126 illustrations. St. Louis: The C. V. Mosby Company, 1928. Price, \$5.00.

IN the words of its preface this book is "an exhibition of the information gained in a clinic, the intimate fusion of data acquired by a physician, a surgeon, and a radiologist with the assistance of a chemist," and perhaps no better description of the work can be given. As the expression of the clinical experience of three experts in separate fields working together in the University of

Paris, it is an unusual and noteworthy contribution to the literature on gastroenterology. In particular the book deals with the subject of periduodenitis, the nature of the duodenum in calculous cholecystitis, and the compression of the duodenum by the mesenteric pedicle—all subjects which have heretofore received scant attention. The discussion of these subjects is both illuminating and thought-provoking, though that of the mesenteric pedicle is perhaps less convincing than the others. There is a helpful chapter on the radiological evidence of duodenal ulcer, and one on the surgical technique of duodenojejunostomy. Throughout the book the duodenum appears in a new light: it is no longer thought of simply as a section of the small intestine, but is raised to a position of importance and treated as an entity. A reading of the book leaves one with a clearer conception of the affections of the duodenum, and raises the hope that a number of hitherto obscure ailments of this section of the gastrointestinal tract may be amenable to successful treatment. It closes with an excellent bibliography.

K. A.

LABORATORY DIAGNOSIS AND EXPERIMENTAL METHODS IN TUBERCULOSIS. By HENRY STUART WILLIS, M.D., Johns Hopkins University and Hospital; with a chapter on Tuberculo-complement Fixation, by J. STANLEY WOOLLEY, M.D., Loomis Sanatorium, Loomis, N. Y.; Introduction by ALLEN K. KRAUSE, M.D., Johns Hopkins University. Pp. 330; 25 illustrations. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1928. Price, \$3.50.

THIS compact and neat little volume ably and invitingly treats of tuberculosis from the laboratory standpoint, presenting in readily available form a wealth of valuable material, with much technical detail ordinarily widely distributed. It is also helpful to the clinician, and shows how he can effectively coöperate with the laboratory. The subjects dealt with include: the examination of the various bodily fluids and secretions, the methods of staining and concentrating tubercle bacilli, animal inoculation and the preparation of culture media. The three types of tubercle bacilli and various nonpathogenic acid-fast bacilli are described. Tuberculin tests and tuberculo-complement fixation and other serologic tests are discussed as to their clinical application and value, and the preparation of materials is given. Anatomic methods, for example, by injection of tissues and by tissue culture, are presented. Allergy and immunity are briefly discussed. Much space is devoted to the study of induced tuberculosis in animals, and the different results in guinea pigs and rabbits are contrasted. About a third of the book deals with histologic technique. Laboratory equipment is outlined. An extensive and valuable bibliography and an index are appended.

Under resistance of the tubercle bacillus something might have been said of the effect of chemicals in gaseous form. Potassium iodid to produce tubercle bacilli in the sputum is not objected to. With Abraham Lincoln and Herbert Hoover the author inclines to the split infinitive.

Filled with information, convenient for reference and available for experimenter and routinist, this excellent book by a recognized authority promises to receive a hearty welcome. C. M.

A HISTORY OF PATHOLOGY. By ESMOND R. LONG, Professor of Pathology, University of Chicago. Pp. 291; 55 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, \$5.00.

IF we accept one of the best definitions of pathology—that it is the study of the effects produced on the body by disease—then its history might easily become coëxtensive with the history of medicine. The author has avoided this pitfall and yet has delved far enough into the roots and borderlines of the subject to exhibit a broad viewpoint and to trace its logical development through the centuries. Incidentally we would have gladly learned when the word pathology first came into use; of course, many centuries before the subject was first recognized as a specialty.

The approach is much the same as in Garrison's *History of Medicine*, to which the author gives high praise. The twelve chapters are devoted to The Pathology of Antiquity; Galen and the Middle Ages; The Pathology of the Renaissance; The Seventeenth Century; Morgagni and the Eighteenth Century; The Paris School at the Opening of the Nineteenth Century; Pathology in England in the First Half of the Nineteenth Century; Rokitansky and the New Vienna School; Virchow and the Cellular Pathology; Pathological Histology and the Last Third of the Nineteenth Century; The Rise of Bacteriology and Immunology and Experimental and Chemical Pathology.

The past century occupies about one-half of the text. The subject matter is well chosen and apportioned, the style forcible, clear and easy and the illustrations are appropriate and for the most part fresh and interesting. Some have unfortunately suffered in the reproduction. "Here is the first definite and systematic account of the subject in English and [that] our author has succeeded in the execution of his plan through his competence, his praiseworthy industry and a spirit ever ready to correct errors pointed out or ascertained." (F. H. Garrison in the Foreword.) We agree absolutely with this and also with the author's statement in the Preface that "nothing gives a better perspective of the subject than an appreciation of the steps by which it has reached its present state."

E. K.

BOOKS RECEIVED.

NEW BOOKS.

*Annals of the Pickett-Thomson Research Laboratory, Volume IV, Part 1. The Pathogenic Streptococci. An Historical Survey of Their Role in Human and Animal Disease.** Pp. 250. Baltimore: Williams & Wilkins Company, 1928.

*Thromboangiitis Obliterans.** By GEORGE E. BROWN and EDGAR V. ALLEN, collaborating with HOWARD R. MAHORNER. Pp. 219; 62 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, \$3.00.

European Clinics. By Editorial Staff of European Clinics, DR. WILLIAM LINTZ, Editor-in-Chief. Pp. 347; illustrated. Philadelphia: J. B. Lippincott Company, 1928. Price, \$5.00.

A report of the clinics given the 125 doctors comprising the Interstate Post-Graduate Assembly of North America, during their visit to England, Scotland, Norway, Sweden, Denmark, Germany and France in 1927. An enthusiastic introduction by the editor stresses the high value of the clinics, which were given by men of high-caliber, covering a wide range.

*Mineral Waters of the United States and American Spas.** By WILLIAM EDWARD FITCH, M.D. Pp. 799; 37 illustrations. Philadelphia: Lea & Febiger, 1927. Price, \$8.50.

*Partnership, Combinations and Antagonisms in Disease.** By EDWARD C. B. IBOTSON, M.D. (LOND.), B.S. Pp. 348. Philadelphia: F. A. Davis Company, 1929.

*The Kahn Test. A Practical Guide.** By R. L. KAHN. Pp. 201; 7 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, \$4.00.

*The Fuel of Life.** By JOHN JAMES RICKARD MACLEOD, M.B., LL.D., D.Sc., F.R.C. Pp. 147. Princeton: Princeton University Press, 1928. Price, \$2.50.

*Diabetic Surgery.** By LELAND S. MCKITTRICK, M.D., F.A.C.S., and HOWARD F. ROOT, M.D. Pp. 269; 81 illustrations. Philadelphia: Lea & Febiger, 1928. Price, \$4.25.

*Contribution a l'Étude des Spirochetides.** By DR. AUGUSTE PETTIT. Pp. 651; 154 illustrations. Vanves (Seine) Chez l'Auteur, 1928. Price, \$4.00.

*Diseases of the Blood.** By A. PINEY, M.D., M.R.C.P. Pp. 195; 20 illustrations. Philadelphia: P. Blakiston's Son & Co., 1928. Price, \$4.00.

Progressive Medicine. Volume IV, December, 1928. Pp. 424; illustrated. Philadelphia: Lea & Febiger, 1928.

NEW EDITIONS.

Alcohol: Its Action on the Human Organism. Issued by the MEDICAL RESEARCH COUNCIL. Distributed in United States by BRITISH LIBRARY OF INFORMATION, 5 East 45th Street, New York City. Second edition, 1928. Pp. 170. Price, 30 cents.

A nonpartisan representation by eminent investigators.

* Reviews followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Heart during Anesthesia.—MARVIN (*New England J. Med.*, 1928, 199, 547) discusses in a very interesting paper the question of operation upon the patient with the damaged heart. This is a perennially active subject of discussion among surgeons and physicians, and the author, from his experience in a large number of heart cases, draws conclusions which seem to be most sane and sensible. In a certain number of cases operation is a necessity in order to save the patient's life, and the cardiac condition must be considered from the point of view of doing all that can be done without injury to the organ. In a goodly number of cases, however, operation might be of great benefit to the patient, although not indicated absolutely. Under such circumstances it should be borne in mind that when a patient is able comfortably to carry on the activities of a normal life the examination which discloses a damaged heart should not alter the decision as to operation. On the other hand, if early congestive failure is present, basing the decision largely on the subjective symptoms of the patient, then the query arises as to whether to operate or not. In these patients, with proper teamwork between the surgeon and physician, operation can be safely carried through to successful termination. Even in patients with advanced congestive failure, rest, digitalis and diuretics will make the operation successful. The choice of the anesthetic to be given to a heart patient is important, but here, almost as nowhere else is it necessary to employ a skilled anesthetist. Nitrous oxid and ethylene are the anesthetics of choice. When given properly there is absolutely no stress or strain on the heart, and the patient comes through without very much more cardiac strain than if he had sunk into a quiet

and restful sleep. Three cardiac conditions are likely to cause sudden death even when the patient is at rest. Syphilitic heart disease with aortic insufficiency, angina pectoris and heart block are cardiac disabilities which should be considered seriously when operation is required. The patient should be warned that sudden death might occur at any time and the slight stimulus of operation might be sufficient to bring about a fatal termination.

Bronchography According to the Passive Technique: the Method of Choice for the Roentgenologist.—OCHSNER (*Radiology*, 1928, 11, 412) refers briefly to attempts of the past to visualize the alignment of the tracheal-bronchial tree and then discusses the indications for bronchography. The methods that we employ at the present time are, for the most part, rather difficult in technique, and those which are not difficult in technique require the coöperation of a bronchoscopist. The method which he uses is technically simple and can be done by any individual. The mouth is cleansed with an antiseptic mouth wash and then the anterior surface of the anterior tonsillar pillar is painted with a 10 per cent cocain solution, from the uvula to the angle between the anterior pillar and the tongue, anesthesia being continued until the swallowing reflex is abolished, as shown by immobility of the larynx upon attempted deglutition. The patient is then given 3 to 4 cc. of a 3 per cent novocain solution. He is instructed to tip the head backward, protrude the tongue and breathe. Novocain acts as an anesthetic to the tracheo-bronchial mucosa. The anterior pillars are again painted with a 10 per cent cocain solution, and the patient placed behind the fluoroscopic screen. He is given 10 cc. of iodized oil in a glass, the head is held backward and he is instructed to take a deep breath and while inhaling pour the oil into the mouth. With the abolition of the swallowing reflex, the oil may be seen flowing from the trachea down to the bronchial tree. An additional 10 cc. is given and in a minute or two it may be seen filling the bronchi, the smaller bronchi and the bronchioles. Confirmatory evidence may be obtained and permanent record made by taking a roentgenogram. The method is extremely simple and may be carried out by anyone who has had no special training with intralaryngeal manipulation. Furthermore, the mode of filling may be observed under the fluoroscope and yields valuable diagnostic information. The method may be also used for the treatment of bronchiectasis and was found to give very excellent results in a considerable series of cases.

Infection of Laboratory Worker with *Bacillus Influenzæ*.—WALKER (*J. Infect. Dis.*, 1928, 43, 300) writes that Pfeiffer's bacillus is frequently present in respiratory-tract infections. It is difficult, however, to determine whether the organism is the primary cause of infection. In the present report an accidental infection with *Bacillus influenzae* occurred in a laboratory worker. The course of the infection is described. Rhinitis, conjunctivitis and bronchitis were the outstanding features. There was no fever. The course of the infection demonstrates that certain strains of the "organism," at least, have an extraordinary avidity for attacking the respiratory mucous membrane as the primary cause of disease.

SURGERY

UNDER THE CHARGE OF

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Congenital Malformations of the Mesentery—A Clinical Entity.—

—WAUGH (*Brit. J. Surg.*, 1928, 15, 438) says that congenital malformations of the mesentery are a definite morbid entity of a chronic type which may be recognized before operation by careful clinical investigation. The symptom complexes to which they give rise cannot be explained by reference to any of the well-known abdominal surgical diseases. The most important physical sign is emptiness of the right iliac fossa associated sometimes with an asymmetrical enlargement of the abdomen on the left side. These signs follow of necessity, inasmuch as the whole segment of the embryonic midgut is involved in a failure of rotation and fixation after reduction from the umbilical sac. Radiological investigation should prove to be more helpful in confirming the clinical diagnosis when the special method of barium by mouth for the small intestines and a concomitant barium enema for the large bowel is followed routinely. Operative treatment may cure the patient; alternately it may reveal a pathologic condition for which a rational course of treatment may be drawn up subsequently, when the precise details of the malformation have been discovered.

Cholecystitis—A Clinical and Experimental Study.—

WILKIE (*Brit. J. Surg.*, 1928, 15, 450) claims that in the vast majority of cases of chronic cholecystitis in the human subject, the bile is sterile on culture. Cultures of the whole thickness of the gall-bladder wall most frequently give no growth. Cultures from the submucous and outer coats, leaving the mucosa intact, have given a growth of streptococci in 42 per cent of cases. Bile has been shown to inhibit the growth of these streptococci. The lymph gland along the cystic duct in cases of cholecystitis has been shown to yield a growth of streptococcus in 86 per cent of cases. *Bacillus coli* was recovered from the bile in only 6 per cent of cases. In the one case in which this organism was recovered from the cystic gland contamination by bile could not be excluded. The streptococcus of cholecystitis is a short-chained type, produces smooth, non-hemolytic colonies on agar and grows readily on glucose broth. Injections of saline suspensions of this organism into the lumen of rabbits' gall bladder produced no change. Intramural injections of streptococci into rabbits' gall bladders produced a progressive chronic cholecystitis from which the organism was readily recoverable. With the cystic duct ligated intramural injections produced a chronic empyema with marked intramural changes. Small calculi were produced with

both types of intramural injection. When the cystic duct was ligated, the calculi contained calcium and cholesterin, when the cystic duct was patent—cholesterin only. Intravenous injection of the streptococci, when repeated, produced a progressive chronic cholecystitis with the formation of cholesterin stones. Separation of the gall bladder from the liver with interpolation of the omentum to exclude infection by lymph spread from the liver, along with ligation of the cystic duct, did not prevent the development of cholecystitis when streptococci were injected intravenously. The intramural pathologic changes produced experimentally, resemble in every detail the changes seen in the human gall bladder in cholecystitis. Cholecystitis would appear to be a blood-borne streptococcic, intramural infection.

Exostoses Occurring in the Os Calcis as the Result of Gonococcal Infection.—WADE (*J. Uro.*, 1928, 20, 259) claims that primarily the causative organism is the gonococcus. Dorsey reports that the gonococcus has been found in spurs. The present author, however, has failed to demonstrate the organism in the osseous deposit. The pathology that occurs is evidently first a periostitis occurring at or near the attachment of the plantar fascia and the attachment of the tendo Achilles followed by a deposit of calcium salts in the sheaths of the tendons. Some contend that a bursitis is the primary pathology with the subsequent spur formation. Many of the patients who are badly disabled by gonorrheal rheumatism are truly sufferers of gonorrheal spurs and after all of the infection in the genitourinary tract has been eliminated, the existing disability may be terminated by removal of the spurs. For a complete recovery after operation the patients must have the focus of infection entirely removed. Spurs may quickly recur in the event of a subsequent infection. Trauma and flat feet play an important part in the production of spurs. Spur formation can be prevented in the stage of periostitis by placing the parts at rest and by well directed local treatment. Sodium iodid intravenously is of great service in this stage. The incision of choice is the one directly down upon the point of pathology.

Thyroid Adenomata.—ROGERS (*Am. J. Surg.*, 1928, 5, 265) claims that there are two varieties of thyroid adenomata: (a) True, interstitial or fetal and (b) pseudovesicular or colloid, "colloid nodules." These terms have regard for the nature and probable origin of the tumors. The fetal tumors occur in young subjects and are hard encapsulated bodies either single or multiple. They are true blastomata. The colloid nodules occur in older women; they are always multiple. They are not true blastomata, but degeneration nodules which become encapsulated by a process of vesicles distended with colloid in groups, intervening between which other vesicles are compressed and distorted until ultimately they form capsules around each of the growing nodules. Either variety of adenoma may become cystic. Adenoparenchymatous goiter is very common. It almost invariably occurs in women. This form may be toxic and may produce pressure at the root of the neck. One or both thyroid lobes may be affected. Adenomata, whether occurring singly or in numbers, are treated by resection—enucleation, the essential details of which procedure are given in the paper.

THERAPEUTICS

UNDER THE CHARGE OF

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Cistern Puncture in the Treatment of Cerebrospinal Meningitis.—

Following upon the work of Ayer, Hartwich, Peet and others, PALSCO (*Wien. klin. Wchnschr.*, 1928, 41, 1182) reports his experiences in the successful treatment of two severe cases of cerebrospinal meningitis by cistern puncture and the injection into the cistern of antimeningococcus serum. Only four other cases similarly treated were found by him in the literature. He discusses the rationale of this method of treatment emphasizing the fact that it assures an effective and complete distribution of the serum throughout the subarachnoid spaces of the brain and even into the brain, ventricles which is not the case following serum administration by lumbar puncture. He says that the method proves comparatively simple, especially when opisthotonus has not developed to a degree sufficient to prevent placing the patient in a sitting position. Not only is the serum distribution more complete and effective than by lumbar puncture, but drainage also is more effective, and in those cases where a block has developed it would seem to be the only satisfactory method of treatment. Injection of serum into the cistern does not seem to be associated with danger of injury to the pons or medulla. This method of injection is usually followed by severe headache, sweating and vomiting which, however, rarely last for more than ten to twenty minutes and are not sufficient to outweigh its many advantages.

The Treatment of Syphilitic Diseases Including That of the Central Nervous System with Sulphur Oil.—Following his successful treatment of 4 out of 7 patients with general paresis, SCHROEDER (*Klin. Wchnschr.*, 1928, 7, 1636) endeavors to determine whether sulphur oil has true antisyphilitic actions or whether the beneficial effects in general paresis are due to its property of producing a febrile reaction analogous to that produced by malaria inoculation. He reports several small groups of cases of primary, secondary and tertiary syphilis which he treated by the intramuscular administration of sulphur oil without the use of recognized syphilitic drugs. He concludes from the effects in these cases that sulphur oil has a definite and rather marked specific antisyphilitic action in all stages of the disease. Although this agent brings about a change in the Wassermann reaction from positive to negative, this change is not permanent in all cases. He feels that sulphur oil cannot, therefore, be regarded as a satisfactory agent for the treatment of syphilis when used alone and thinks that it should be used only in conjunction or alternating with recognized antisyphilitics. He notes in addition to its beneficial effects, which seem especially well marked in syphilis of the central nervous system, that it seems to be well borne in the presence of severe vascular disease and in pregnant

women. In the latter, however, it must be administered carefully in order to avoid a marked rise of temperature. In view of the demonstration of antisyphilitic action by sulphur oil, the author raises the question as to how far one should go in the endeavor to produce a marked febrile reaction, although he admits that in certain cases such as general paresis such a reaction is apparently of itself a valuable therapeutic measure.

Alcohol Injection in the Treatment of Gangrene.—HANDLEY (*Brit. Med. J.*, 1928, ii, 593) discusses the value and the serious disadvantages of Leriche's periarterial sympathectomy in the preventative treatment of gangrene, and contends that the periarterial injection of alcohol is equally effective and is devoid of many of the disadvantages of the Leriche operation. The technique is not difficult. The exposed artery is injected at four points around its circumference with 2 to 3 minims of alcohol at each point. The finest possible needle is employed and is introduced obliquely and nearly parallel with the long axis of the artery. This injection produces a white band about $\frac{1}{2}$ inch wide encircling the vessel. The effects are immediate, and the initial constriction present in the Leriche operation is absent, there being no vasoconstriction, but, on the contrary, immediate distal dilatation. This fact is of particular value in cases where gangrene is threatened. The effects of the Leriche operation last for only a few weeks, while the dilatation secured from injection may last for more than a year. The one great disadvantage of alcohol injection is the fact that its results are uncertain, probably due to anatomic differences in the distribution of the vasomotor nerves, so that occasionally no dilatation at all ensues. The indications for its use are not well established, but since it is probably safe its trial is justified wherever it seems to be indicated. It may be recommended in cases of threatened or incipient senile gangrene of a lower extremity, and should, if possible, be employed in the prodromal period. It seems to be useless in Buerger's disease, and is of doubtful use in Raynaud's disease.

Histamin Action and Blood Regeneration.—In an endeavor to throw some light on the problem of the nature of the substance in liver extracts which is responsible for blood regeneration, J. PAL (*Deutsch. med. Wchnschr.*, 1928, 54, 1544) having observed that some of those liver extracts employed for their depressant action on the blood pressure also produced notable blood regeneration, undertook to study other tissue extracts and found that those containing histamin all produced blood regeneration. Similarly, he finds that small doses of histamin itself stimulate the regeneration of the red cells in pernicious anemia, in secondary anemia and even in normal persons. Along with this effect on blood regeneration there is also a stimulation or a restoration of the failing appetite just as with the administration of liver itself or the effective extracts. From these observations, he concludes that histamin is, perhaps the most important, of the substances responsible for promoting regeneration of the blood. He also concludes that blood regeneration is itself the factor that is responsible in anemic and cachectic patients for stimulation of appetite and the improvement in their general well being.

PEDIATRICS

UNDER THE CHARGE OF

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Newer Aspects of Acidosis.—MARRIOTT and HARTMANN (*J. Am. Med. Assn.*, 1928, 91, 1675) state that the contributing factors in acidosis are increase of normal acids such as lactic, phosphoric and sulphuric; the loss of fixed base; and maintenance or failure of maintenance of normal osmotic pressure. The explanation of the means by which such factors operate lies in the effects of dehydration due to diarrhea, vomiting or polyuria; abnormal metabolism giving rise to abnormal organic acids, and failure of the kidney because of oliguria or actual renal injury to adjust by urinary secretion for such changes. Water loss due to diarrhea would naturally be expected to increase the concentration of all solutes in the plasma except those which may be secreted in the gastrointestinal canal and into the urine. In the dehydration accompanying severe diarrhea oliguria occurs, so that loss of solute by the urine may be neglected. There apparently occurs loss of base bicarbonate by way of the bowel because of its secretion from the plasma into the pancreatic and intestinal juices. The early picture of the anhydremia is brought about chiefly by water and base bicarbonate loss in the stool. Where the dehydration is caused solely by vomiting as in pyloric or high intestinal obstruction, there occurs a loss of gastric juice which contains hydrochloric acid and a small amount of fixed base. A dehydration of this sort would give rise to a diminished base chlorid content of the plasma with increase in base bicarbonate or an alkalosis. If dehydration is brought about largely by a polyuria as in diabetes, the urine carries out not only dextrose and water but also important salts. The loss of these substances is important in producing diabetic acidosis. In severe chronic nephritis, urinary secretion is at fault as a result of renal injury, and acids such as phosphoric and sulphuric are insufficiently removed. There also occurs a loss of fixed base from the plasma in excess of the usual loss. This is due to a failure of the kidney to substitute ammonia for the fixed base of the plasma salts and secondarily from failure of the kidney to maintain the normal maximum hydrogen-ion concentration of the urine.

Healing in Infantile Scurvy as Shown by X-ray.—MCLEAN and MCINTOSH (*Am. J. Dis. Child.*, 1928, 36, 875) in a long paper enumerate the types of disturbances found by Roentgen rays of the long bones in infants with scurvy, and describe the changes during the process of healing. In 115 roentgenologic examinations of 52 patients with scurvy particular reference was made to the variation in the picture according to the stage of the disease. The relative value of the Roentgen ray signs of scurvy from the viewpoint of diagnosis in acute cases and the relative frequency of the various signs presented for all stages are shown

in their tabulations. They found it necessary to take the rachitic factor into consideration as its presence often modifies the scorbutic picture. They found a decided tendency for the scurvy to heal by the laying down of new lines of calcification. Hematoma of large size was noted to have left their mark as long as three years in the form of unilateral thickening of the shaft. Disturbances of nutrition may alter the rate though not the general order of the changes. These changes vary from fibrous tissue trabecular changes through to calcification.

The Preventorium Child.—BRONFIN (*Am. J. Dis. Child.*, 1928, 36, 931) reviewed the records of 300 preventorium children and made a study of the roentgenograms. An underweight of 7 per cent or more was found in 70 per cent. In 45 per cent definite cervical or submaxillary lymphadenitis was noted. In 30 per cent, fever was a prominent symptom. An appreciable difference was not observed in the symptomatology or physical signs between the tonsillectomized and the non-tonsillectomized groups. The greatest incidence of clinical disease and positive physical signs was noted in those with a history of definite exposure. Physical signs were often negative when the history and symptoms pointed to active disease. The Roentgen rays were of the greatest importance in diagnosis when correlated with the other symptoms. Of the entire series, only 72 roentgenograms of the chest were considered within the normal. Calcification at the hilum, strongly suggestive of tuberculosis, was observed in only 22 per cent, but it is believed that the incidence would have been greater if films in the oblique position had been taken. Primary foci were detected in 11.6 per cent, and in 11.3 per cent there was noted frank parenchymal pulmonary infiltration. Attention was called to the difficulty in making a diagnosis of tracheobronchial tuberculosis, which in this series was frequently responsible for active symptoms and was often attributed to other causes. Under treatment, symptomatic improvement invariably occurred. Unremitting supervision was necessary for in many patients there was a recurrence of symptoms with increased physical activity. A notable recession was not noted in either the cervical or the tracheobronchial glands after prolonged periods of continued heliotherapy.

A Clinical Study of Enuresis.—BLEYER (*Am. J. Dis. Child.*, 1928, 36, 989) says that a clinical study of certain factors commonly held accountable for enuresis failed to show their relations to this disease. Cures in this series of cases amounted to about 80 per cent and were accomplished without regard to any of these factors by measures directed to the bladder itself. A study of the incidence of enuresis in relation to sex suggests that the cause of this disease does not exist in any anatomic or physiologic peculiarity external to the opening of the bladder. The rôle of the voluntary nervous system is unimportant in enuresis. This disease is a disturbance of the physiology of micturition, probably due to stimuli arising in the bladder itself which for the time being place it beyond the control of the will. Discipline plays no part in true enuresis, since this disease does not owe its origin to a lack of discipline nor is it controlled by this measure. In conformity with the definition evolved in this study, the term *enuresis vera* is suggested to

indicate that type in which dissociation between the brain and the voluntary nervous system, as concerns the physiology of micturition, actually appears to exist, and the term pseudoenuresis is reserved for that type of defective control which can be relieved by measures designed to influence the will or to obtain the coöperation of the child. Atropin and massage of the bladder were the only measures found to be effective in the treatment of true enuresis.

Restlessness in Infancy.—LIPPMAN (*J. Am. Med. Assn.*, 1928, 91, 1848) recommends certain measures to control restlessness in infancy. Every attempt should be made to insure the mother rest and relaxation in a peaceful environment. The presence of the child in the home should not preclude other emotional outlets for the parents. The greater share of the management of the restless infant, as far as is practical and possible, should be turned over to other persons than the parents. Frequent dietary changes may be necessary before the ideal food or schedule can be realized. Every reliable known means of relieving air swallowing should be utilized, even to the extent of temporary removal from the breast. The measure of placing the infant to the breast in a drowsy sleepy state should be employed. The suggestion of using chloral to produce this sleepy state should be considered. Atropin should be used. The author urges its use up to the point of tolerance.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Alopecia Areata.—PUSEY (*Arch. Dermat. and Syph.*, 1928, 17, 701) has recently briefly reported a case of alopecia areata apparently the sequel of severe emotional stress and nervous shock.

Industrial Dermatoses.—The lesions are classified by FOERSTER (*Arch. Dermat. and Syph.*, 1928, 17, 585) into toxicodermias, involving a sensitization factor, localized occupational dermatitis, limited to sites of contact with the irritant, and occupational eczema, which persists, extends and recurs after the exciting cause is removed. Periodic inspection, physical examination before employment and the building up a selected, resistant personnel in occupations involving irritants are emphasized. Treatment at the onset should be properly planned, for prolonged attacks often follow the injudicious use of irritant routine

first-aid applications. A complete cure of the first attack is important to prevent relapse and chronicity. Cleanliness, obtained by making the clean-up time part of the working hours, has great prophylactic value. The investigation of the systemic background of the individual case is as important in industrial as in nonoccupational dermatoses. "Compensation is not dependent on any implied assumption of perfect health" in the worker. The mere fact of hiring him is a presumption of good health, and his dermatoses of occupational origin are, therefore, compensable even though a predisposing cause antedated his employment. In the discussion of this paper, the influence of carriers and disseminators of pyogenic infection was emphasized, and the value of rotating workers through short periods in jobs involving contact with irritants. The necessity for the dermatologist and the industrial physician knowing the trade processes as well as the medical aspects of industrial cutaneous disease was also stressed.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Kidney Destruction by Irradiation.—One of the most unpleasant sequels of the radical operation for the removal of uterine cancer is the development of a urinary fistula as the result of injury to one of the ureters. If the fistula does not close spontaneously after a fair period of time, there are two choices for the patient, plastic operation on the ureter, including various types of implantation into bladder or bowel, and removal of the corresponding kidney. In many cases an attempt to treat the fistula by a conservative procedure is out of the question on account of the extent of the primary operation and the hazard which would accompany a secondary operation in such a field so that if the patient is to be relieved it must be by removal of the kidney. It has been shown by animal experiments that if sufficient irradiation of the Roentgen rays be given to the kidney, its function will be seriously impaired and finally cease altogether. Applying this fact for the first time to the human being, KLEIN (*Zentral b. f. Gynäk.*, 1928, 52, 1500), of Prag, reports that in 4 cases of ureteral fistula following the Wertheim operation, which could not have been helped except by nephrectomy, irradiation was given to the kidney on the side of the injury and in each case the urinary excretion ceased and the patient became entirely relieved of her trouble. This is a form of therapy which is well worth

remembering because none of us can tell when we might have a case of ureteral injury on our hands in which the risk of further surgery might be attended with too much danger and it would be very comforting to know that such cases have been entirely relieved by Roentgen ray treatment of the kidney.

Pelvic Inflammatory Disease.—On several previous occasions, we have discussed the variable views in regard to the surgical treatment of pelvic inflammatory disease and have quoted the opinions of leaders in the profession both in this country and in Great Britain but have apparently overlooked some of the reports coming from Central Europe. It is of considerable interest therefore to refer to a well-prepared report which has been presented by SZTEHLO (*Zentralbl. f. Gynäk.*, 1928, 52, 2233) of Budapest. The report is based upon 233 patients who were operated upon for suppurative pelvic inflammatory disease in his clinic, of which Lovrich is chief, during a period of fourteen years. In the acute stage of the disease, they do not operate except upon vital indications. In the chronic stage, they operate upon patients who have been free from any fever for a period of from six to twelve months and then only after a thirty- to forty-minute treatment with diathermy produces no febrile reaction. All of the operations are performed by the abdominal route, never by way of the vagina. In most of the cases that are operated upon, conservative surgery is the rule, only in rare instances is the uterus removed by supravaginal hysterectomy and in no case have they performed complete hysterectomy. In removing the tubes, the wedge excision of the cornual portion is always performed. Vaginal drainage is employed if the abscess sac is ruptured during removal and pus is spilled or when satisfactory peritonealization cannot be accomplished and also in those cases where there is bloody oozing which cannot be controlled by other means. While the blood-sedimentation test has been used frequently to determine when the patient is ready for operation, the results have not by any means been what could be desired since more than half of the patients who died following operation had a sedimentation time of over an hour. He believes that the result of the operation cannot be predicted by any test and does not depend entirely on the virulence of the bacteria, the asepsis or technique of the operation but upon the unknown factor of the resistance of the individual patient. As a demonstration of this point he cites 2 cases which were operated upon on succeeding days for the same condition. Both had the same preoperative preparation, normal blood findings and a sedimentation time of over an hour and gave no febrile reaction following diathermy. At operation bilateral pus tubes were removed in each case. One patient had hemolytic streptococci in the pus and she made an afebrile recovery; in the other patient only sterile pus was obtained but she died on the third day from symptoms of general peritonitis. In this series of 233 cases there were 10 deaths (4.3 per cent mortality) and the operations performed consisted of removal of one adnexa in 19.3 per cent, removal of both adnexa in 61.6 per cent, removal of one adnexa and the opposite tube in 10 per cent and supravaginal removal of the uterus in 9.1 per cent. Satisfactory postoperative results were obtained in 89 per cent of the cases and secondary operation was called for in only one case (0.4 per cent). The good postoperative results are

largely attributed to the frequent employment of vaginal drainage, it having been employed in over half of the cases. The following table, presenting the mortality experience of several European clinics will be of interest to the American gynecologist:

	Per cent mortality.
Thaler, 108 radical operations	8.6
Thaler, 262 conservative operations	5.3
Werner, 193 radical operations	6.7
Werner, 94 conservative operations	2.1
K. Fraenkel, 372 radical operations	6.6
Frigyesi, ? radical operations	7.5
Frigyesi, ? conservative operations	4.5

Sarcoma of the Uterus.—In an investigative search for information relative to sarcoma of the uterus MILLER and ROGERS (*New England Med. J.*, 1928, 198, 927) have gone over the records of the Massachusetts General Hospital for the period from 1876 to 1926 and found 25 cases of sarcoma of the uterus, constituting 1.4 per cent of the number of uterine fibroids which were observed during that time. They found that sarcoma of the uterus presents no pathognomonic signs or symptoms and is usually mistaken for myoma. It may, but does not necessarily originate in a preëxisting myoma but any rapidly growing fibroid tumor should be suspected of being sarcomatous. At every operation for fibroid tumor the specimen should be carefully examined to determine if sarcoma be present and if so the operation should be made very radical. In this series the chief symptoms were bleeding in 68 per cent, pain in 52 per cent, abdominal tumor in 40 per cent and loss of weight in 12 per cent. In the follow-up study, 48 per cent were not traced and but 4 per cent were well six years after the operation.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Ocular Complications of Diabetes.—GIFFORD (*Med. Clin. North America.*, 1928, 12, 423) states that true diabetic cataract may occur, but is rare, while senile cataract occurring in the diabetic is common and does not differ from cataract in the nondiabetic. With a little preoperative care to reduce the urinary sugar to the minimum, operation in these cases is not attended by any great risk. What may be called a true diabetic cataract is characterized by the appearance of fluid vacuoles under the capsules of both lenses, which progresses rapidly to complete opacity in periods of a few weeks to six months. There may be an occurrence of changes in refraction during the course of diabetes. When the blood sugar becomes suddenly high, the osmotic pressure of the

blood becomes low through the pouring of the fluid into the blood from the tissues and the loss of sodium chloride from the blood. This fluid of low osmotic pressure is able to penetrate the lens capsule, causing the lens to swell, with resulting myopia. If blood sugar is lowered, the lens gives up the water, becomes flatter than normal, with resulting hyperopia. The serious change in diabetes is diabetic retinitis. Two types of lesions are seen, white patches which are usually small and single, seen in the central region and around the nerve. Hemorrhages along large vessels are not far from the nerve head. The author refers to the paper of Wagener and Wilder, they reporting that retinitis was not seen in the severe forms of pure diabetes but the mild, easily controlled cases with some evidence of vascular disease, and the retinitis was due to arteriosclerosis. Author finds nothing in this article on which they based their findings as to the vascular origin of the retinitis. Since this report American ophthalmologists may have been inclined even to doubt the existence of pure diabetic retinitis. The presence of retinitis in a diabetic does not indicate a particularly grave prognosis in cataract as does albuminuric retinitis.

Oculogyric Crises in Chronic Epidemic Encephalitis.—McCOWAN and COOK (*Brain*, 1928, 51, 283) state that it is doubtful if the tonic eye spasms, termed by the French, crises oculogyres, occurred before 1923. The incidence of these cases is increasing. In this series of 23 cases taken from a total of 136 cases of encephalitis the earliest case commenced in 1923 and the earliest epidemic which led to a case was that of 1919. The shortest interval between the acute attack and the appearance of the crisis has been a few months and the longest eight years. All cases are associated with Parkinsonism, the onset preceding that of the crises. Age and sex are unimportant. Other ocular symptoms are not more frequent than in ordinary encephalitis without crises. The crises are in the nature of tonic seizures not always confined to the eye muscles but frequently involving the muscles of the head and neck. Pain is an unusual concomitant, but physical distress of various kinds is very common. The eyes may become fixed in any position and this position may change during a crisis or between crises. In one case the eyes took a position of forced convergence and in three a fixed stare to the front. This variability is important in determining the site of the lesion. The most common position is either straight up or upward and to either side. The eyes may remain fixed from a few seconds to several hours. Fatigue is an important factor in the onset of the attacks because they occur most often in the afternoon or evening. Usually there is no obvious exciting cause. It is occasionally possible to shorten or prevent attacks and suggestion is the most potent agent in this respect but it is misleading to regard these cases as hysterical in nature because the increased suggestibility of the encephalitis is due to an interference with normal cortical control and a cutting off of its inhibitory influence. The casual lesion of oculogyric crisis lies in associational mechanism situated above the four supranuclear centers subserving conjugate movements the theory being accepted that there is a supranuclear center for lateral conjugate movements and one for vertical movements on each side. In a certain number of cases the crises tends to disappear with time and this is especially true in those treated with hyoscin hypodermically.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Gross and Microscopic Pathology in Twenty-three Consecutive External Frontal Ethmosphenoid Operations.—SIMPSON and HARRIS (*Ann. Otol., Rhinol. and Laryngol.*, 1928, 37, 452) found in all cases a hyperplastic submucosa infiltrated with all types of acute and chronic inflammatory cells, as well as periosteal thickening. Most cases revealed many submucosal thrombotic bloodvessels. In several instances ulceration of the mucosa was seen. Metaplasia occurred in those cases of prolonged chronic irritation. Grossly, of the 23 cases, periostitis occurred in 20, polypi in 12, osseous necrosis to point of perforation in 3, cysts in 2, and osteoma in 1. A brief résumé of each case is given. Some of the cases, which were clinically chronic, were found to present microscopic evidence of acute inflammation, and, *vice versa*, in one acute case much evidence of chronic pathological change was encountered. The authors believe that some acute processes are only acute exacerbations of a chronic condition.

Cystologic Examination in the Diagnosis of Infection in the Nasal Accessory Sinuses.—Convinced that the macroscopic examination of washings from the paranasal sinuses is not a trustworthy diagnostic procedure, and basing the rationale of his method on the fact that cellular elements are absent in the irrigating fluids from normal sinuses, SEWALL (*Ann. Otol., Rhinol. and Laryngol.*, 1928, 37, 642) describes the technique of irrigation of the maxillary sinus as a means of obtaining material for microscopic examination of the antral contents. In the interpretation of the cytological picture on the glass slides as indicative of the pathologic lesion in the sinus, he relies on the predominance of polymorphonuclear leukocytes as pointing to an acute inflammatory process, and of mononuclear forms as suggesting less acute inflammation. Certain technical sources of errors are discussed. The author states that, although the method may become a useful diagnostic procedure in all the paranasal cavities, he has employed it in only the maxillary and sphenoidal sinuses. He considers it as an adjunct in diagnosis of sinus disease, along with such other important aids as history, symptoms, physical findings and Roentgen ray.

Otologic Observations in Trauma of the Head. A Clinical Study Based on 42 Cases.—Disregarding their medicolegal aspects, injuries to the head comprise a most important and alluring field in medicine and surgery—a field which, either directly or indirectly, embraces virtually all departments of medical activity. In analyzing the otologic manifestations in a series of 42 cases, GROVE (*Arch. Otolaryngol.*, 1928, 8, 249) discusses various mechanical, anatomic, pathologic and clinical phases of head traumata. He emphasizes the importance of examination

as soon after the injury as possible, and also at regular intervals over a considerable period. The severity of the trauma does not bear any direct relation to the development or degree of cochlear and vestibular symptoms. Within the temporal bone hemorrhages were found to be the outstanding lesion. Hemorrhage from one or both ears occurred in 9 cases and indicates a longitudinal fracture of the temporal bone. Such cardinal symptoms of vestibular injury as vertigo and spontaneous nystagmus were encountered and carefully analyzed. Deafness was complained of in 14 instances and was found in 31, of which 28 had symptoms referable to the vestibular apparatus. Complete unilateral deafness occurred once. Headache was the commonest complaint.

RADIOLOGY

UNDER THE CHARGE OF

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Cholecystography.—From their experience with the oral method in 1500 patients, LOCKWOOD and SKINNER (*Radiology*, 1928, 11, 7) conclude that neither hyperchlorhydria nor achlorhydria have any effect on the shadow of the gall bladder. In 70 per cent of the patients with pernicious anemia cholecystography indicated disease of the gall bladder, 39 per cent having stones; several of the patients improved after operation. Of patients having myocardial degeneration 71 per cent responded abnormally to cholecystography. In cases of infectious arthritis, 69 per cent had cholecystographic evidence of gall bladder disease and 15 per cent exhibited shadows of stones.

Metrosalpingography with Iodized Oil.—Introduced by Sicard and Forestier in 1922, the roentgenography of the uterus and tubes after injection of iodized oil has been of great service. RUBIN and BENDIC (*Am. J. Roent. and Rad. Therap.*, 1928, 19, 348) remind the reader that by this means the uterus and tubes are not seen, but a perfect cast of their cavities is demonstrated. The uterine cavity is triangular in shape, the intrauterine diameter averaging about 4 cm. in width, the narrowest portion being at the internal os. The length of the uterine cavity is about 5 cm. when the uterus is subjected to a pressure of about 100 mm. of mercury. The tube consists of two parts—the isthmus and the ampulla. The isthmus is divided into an intramural portion and the isthmus proper. The ampulla can be divided into the ampulla proper and fimbria (or infundibulum). The short intramural portion of the tube varies from 0.5 to 1.5 cm. in length and is often constricted

at each end. It usually curves downward and outward but the writers saw no multiple curves and angles as described by certain authors. The isthmus proper is seen as a narrow band, often hairlike, sometimes 2 mm. broad. It varies in length from 3 to 10 cm., the average being about 5 cm. Its direction is usually downward and outward and it seldom exhibits any angulations. The ampulla is much wider and always appears irregularly coiled. Its usual width is about 5 mm. and in length it varies from 4 to 10 cm. The fimbria can be seen as a triangular mass, often having on one side a concavity corresponding to the surface of the ovary.

Radium Treatment of Tonsils.—Comparing radium treatment with tonsillectomy, WILLIAMS (*Am. J. Roent. and Rad. Ther.*, 1928, 19, 334) thinks that the advantage rests with the former. Tonsillectomy entails the use of an anesthetic and the shock of operation; other tissues may be removed; hemorrhage, infection or great soreness in the throat may result, and a week or more may be required for recovery. Radium treatment avoids the use of an anesthetic and is painless; causes no shock, hemorrhage, infection, or pulmonary complications, and the patient's occupation is not interrupted. Radium has a wider field of usefulness than that covered by tonsillectomy in that it can be employed for patients who are not good operative risks, and, what is also important, for treating diseased lymphoid tissue in the pharynx and other parts of the throat. When radium treatment is available and can be carried out properly, tonsillectomy, as a rule, should not be done.

Physical Therapy in the Treatment of Illnesses Caused by Light, Heat, Cold, Mechanical Irritation, etc.—In the treatment of certain diseases, set rules may be given for the application of physical agents, such as light, heat, cold and mechanical irritation which apply to the average individual and enable one apparently to obtain maximum benefit with a minimum of harmful result. In this paper by DUKE (*Arch. Phys. Ther., X-ray, Radium*, 1928, 9, 193) are described cases which show that such rules cannot be applied universally. Some individuals are highly sensitive to the action of one or more of the physical agents mentioned. In these the application of physical agents in average dosage causes harmful and even dangerous results. Illnesses in patients of this type caused by physical agents as they are encountered under natural conditions are often extremely severe. The symptoms observed can be classified under such terms as urticaria and dermatitis of greatest severity, rhinitis, cough or asthma, gastrointestinal disturbances of mild or extreme grade, urological disturbances, such as irritable bladder or even renal colic. The fact is, that few tissues are immune to disturbance caused by the effect of physical agents in sensitive individuals. The illnesses are extremely specific and are caused in a given individual usually by one and only one specific physical agent. For example, those caused by light, may be caused by certain rays of light at the violet end of the spectrum and by light only. In those sensitive to cold, symptoms may appear only after exposure to cold between certain specific grades, such as between 5° and 15° C. Brilliant therapeutic results can be obtained through the avoidance of the agent to which the patient is sensitive or through the appropriate application of the

agent in repeated gradually increasing dosage. This frequently gives rise to tolerance. For example, through the use of increasing dosage of light in light sensitive cases, cold in cold sensitive cases, heat in heat sensitive cases or of friction in friction sensitive cases a degree of tolerance can frequently be obtained which enables the patient to withstand such dosage as he encounters under natural conditions—in fact, the agent previously harmful after treatment usually becomes beneficial.

The Roentgenogram in Mastoid Disease.—While emphasizing the substantial aid of roentgenography in mastoid diagnosis, TAYLOR (*Am. J. Roent. and Rad. Therap.*, 1928, 19, 522) insists that it should not outweigh the clinical findings and the latter should furnish the chief guide to procedure. A history of a previous acute otitic infection must be taken into consideration in estimating the significance of a localized area of destruction shown by the roentgenogram. A mastoiditis which shows only mild involvement, as evidenced by decreased illumination and slight destructive changes may clear up without operation. Progress of destructive changes in an acute otic infection indicates that the lesion is active.

Insufflation of Carbon Dioxid in the Roentgen Diagnosis of Tubal Obstruction.—From experience with 66 patients, RUBIN (*Radiology*, 1928, 11, 115) strongly prefers insufflation with carbon dioxid to the injection of iodized oil for determining the patency of the Fallopian tubes. The gas demonstrates tubal patency or nonpatency, and is rapidly resorbed without trace. It is practically innocuous, is simpler to carry out than the injection of lipiodol, although having diagnostic value equal to the latter, and is superior to lipiodol for demonstrating tubal spasm.

Roentgen Ray Diagnosis of Pulmonary Infection with the Friedländer Bacillus.—KORNBLUM (*Am. J. Roent. and Rad. Therap.*, 1928, 19, 513) holds that Friedländer's pneumonia, which is probably more common than is generally supposed, presents a characteristic roentgenographic appearance, with four definite stages. In the initial stage it greatly resembles ordinary bronchopneumonia, but differs from the latter in that it seldom has a typical, bilateral, basal distribution, and the involvement is most marked peripherally. In the second stage, the bronchopneumonic areas coalesce and imitate lobar pneumonia, except that the consolidations do not follow the anatomic markings of the lobes, and resolution begins at the hilum. In the third stage, which is most characteristic roentgenologically, abscesses, many of which have a demonstrable fluid level, develop in the consolidated areas. Following survival of the third stage the process gradually assumes a chronic nature. An irregular fibrosis occurs with cavities remaining at the site of the previous abscesses. The cavities are thin walled and sometimes difficult to detect. During this period reinfections may occur, the same or new areas passing through virtually the same stages *de novo*.

Roentgen and Radium Treatment of Toxic Goiter.—For toxic goiter STEVENS (*Am. J. Roent. and Rad. Therap.*, 1928, 19, 539) considers that radiation with Roentgen rays or radium is second to no other method of treatment and may be expected to cure about 90 per cent of the patients.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Intractable Chronic Pain in the Lower Segments of the Body. Relief by Means of Sacral Epidural Injections.—Viner (*Arch. Neurol. and Psychiat.*, 1928, 20, 336) outlines the technique of epidural injection and reports on its use for the relief of pain in sciatica, lumbosacral pain, rheumatoid arthritis, locomotor ataxia, cancer of the rectum, encephalitis, coccygodynia, amputation stump neurologia, traumatic neuritis, endarteritis obliterans, diabetic ulcer of the leg and tumor of the spinal cord. (The author questions this diagnosis.) He concludes that the treatment is effective in the worst and most persistent cases of sciatica, is of decided value in tabetic lightning pains and in many of the other conditions mentioned. "In general, it seems correct to say that this method is efficient in all kinds of chronic peripheral pain originating at or below the third lumbar segment which is not of vascular or sympathetic origin." He warns that in those cases where the injection proves satisfactory the patient should not be discharged as the causal condition may appear later and may require appropriate treatment.

Central Neuritis, its Etiology and Symptomatology.—PEARSON (*Arch. Neurol. and Psychiat.*, 1928, 20, 366) reports 31 cases found with clinical diagnoses as follows: Involutional melancholia, 2 cases; manic depressive psychosis, depressed type, 2; manic depressive psychosis, mixed type, 2; undiagnosed, but probably toxic exhaustive psychosis, 1; psychosis with somatic disease, 5; senile dementia, 1; schizophrenia, paranoid type, 1; chronic alcoholism, 4; delirium tremens, 2; pellagra, 9; probable pellagra, but diagnosed general paralysis, 1; epilepsy, 1. As to symptomatology and course of the disease, he found that these cases did not differ materially from unselected cases of the analogous symptom complex without central neuritis except in the cases of pellagra in which disease every case showed the pathologic changes. He discusses the possible causes and concludes that it is not caused by axonal injury, infection, starvation, exogenous or known endogenous toxins, nor is it a prelethal condition. "It seems to be the result of some subtle disturbance of metabolism that produces starvation and autometabolism of the cell." He states that the names applied to this condition are misnomers and advances "primary cytolytic degeneration" as a preferable term.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Splenic Mycosis.—Splenic mycosis presents a gross picture characterized by the appearance of yellowish-brown firm nodules found in the trabeculae of the spleen. They vary in shape and may be scarcely visible or measure several millimeters in diameter. By fusion large infarct areas may be formed. The color of these nodules is chiefly due to the iron pigment, the pigment may become embedded in sclerosed tissue, some nodules may become calcified, the whole area is surrounded by recent hemorrhage. By investigation, JAFFE and HILL (*Arch. Path.*, 1928, 6, 196) have shown the siderotic nodules of the spleen to contain mycelium and fructification bodies of an aspergillus. This finding has also been found in juvenile splenomegalic anemia, sickle-celled anemia and in tuberculosis of the spleen. It would appear that different types of aspergillus would produce similar changes. The occurrence of the fungus under different types of pathologic conditions does not favor the theory of a disease entity caused by a fungus. Patients have been encountered with splenic anemia whose spleens have shown fungi. Others with the same disease show no fungi. On the other hand, fungus has been found in cases which have splenomegaly without anemia, hence the fungus is not responsible for the anemia. The reactions of the body against the fungus are foreign-body giant cells along with a proliferation of connective tissue. The mycelium absorb iron and calcium salts and are finally buried in sclerosed tissue which may then become calcified. In view of the fact that the aspergillus has been found in both large and small spleens the term "splenic mycosis" is preferred to that of mycotic splenomegaly.

Immunization of Children against Tuberculosis.—This problem has been before the medical world since the tubercle bacillus was discovered. The work of Calmette and his coworkers with an avirulent living culture of tubercle bacilli called B.C.G. (*Bacillus Calmette-Guerin*) has aroused a tremendous interest in the subject and about 100,000 infants have been treated as a result. PETROFF and BRANCH (*Am. J. Pub. Health*, 1928, 18, 843) have given an analysis and critical review of the already extensive literature on this topic. They point out that the favorable results reported have been gained largely from impressions and not from facts. It has been shown that from 40 to 90 per cent of children at the age of puberty give a positive Pirquet tuberculin reaction and that the evidence suggests that a high percentage have become infected during the first year of life and in the presence of heavy family dissemination the mortality is high. On the other hand, the ordinary

nonprogressive infection has been considered as responsible for the high degree of resistance in the human race. Because Calmette believes that most infection takes place in the first ten days by the digestive route his vaccinations have all been carried out by feeding the organism to newborn babies. The questions arise: (1) Is it dangerous? (2) Is it effective? The evidence bearing on the pathogenicity of B.C.G. and on the results of vaccination in animals is carefully given and also the preparation of the vaccine and the method applied in infants. The authors' study of cultures of B.C.G. resulted in separating two types of colonies the "R" and "S," the former producing tubercles which heal and the latter progressive disease and death of the guinea pig. They, therefore, suggest that Calmette has by his method of culture permitted the "R" form to predominate without however, completely eliminating the "S" form. The article is full of interesting points on pathogenicity, modes of infection, dissociation, transmutation, filtrable forms and other phases of the problem. The authors consider the other effective sociologic and health measures have decreased the mortality and infection in childhood to a very low level in the United States and Canada and see no reason for introducing this prophylactic measure of vaccination of infants at present. They further say that "The careless use of poor statistics obtained from a study of human beings is going to lead us nowhere" and advocate the study of the problem in cattle on a large scale. . .

The Gastrointestinal Flora in Pernicious Anemia.—In the past the qualitative study of the intestinal flora has been chiefly applied to the acute infections and has given most satisfactory results in the discovery of such specific organisms as those inducing cholera; dysentery, and so forth. On the other hand, little attention has been paid to the organisms normally present in the intestine. DAVIDSON (*J. Path. and Bact.*, 1928, 31, 557) presents the possibility that these latter, if increased in numbers and toxicity, may cause some ill-defined medical conditions or have a pertinent bearing on the development of pernicious anemia. This article is the result of a bacteriologic study, quantitative as well as qualitative, made upon the gastrointestinal contents of 41 cases of pernicious anemia. For the sake of comparison, the flora of healthy subjects and of others, showing various pathologic conditions, was investigated. The actual bacteriologic work done was very extensive and in part very ingenious. No claim is made that accurate numerical results were obtained by the quantitative technique; but in spite of many inconstant elements, the author states that, after examining hundreds of specimens from animals and humans, in any given case the bacterial count will remain within a limited range. The differences between normal and pathologic specimens are so great that all minor errors are eliminated. The quantitative studies showed that the feces in pernicious anemia contain more *B. coli*, more streptococci and especially more *B. welchii* than are present in normal persons or in others suffering from various diseases. Careful study suggests that the *B. welchii* are increased 1000 to 10,000 times over the content in healthy cases. The qualitative studies brought forth no evidence which would indicate that any particular variety of the usual strains was associated with pernicious anemia. The organisms studied were *B. coli*; strepto-

coccus; *B. acidophilus*; and *B. welchii*. In pernicious anemia, high bacterial counts were noted in all gastroduodenal contents, but no specific organism was demonstrable, and *B. welchii* were in relatively small numbers. The author views pernicious anemia as a pathologic rather than an etiologic entity. He looks upon gastrointestinal sepsis as an extrinsic factor which functions by preventing the liver from producing the substance which, as Minot and Murphy have shown, is necessary for the proper maturation of the megaloblasts.

HYGIENE AND PUBLIC HEALTH

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The Action of Currents of Very High Frequency upon Tissue Cells.
A. Upon a Transplantable Mouse Sarcoma.—SCHERESCHEWSKY (*Pub. Health Reps.*, 1928, 43, 927) used a mouse sarcoma strain which gave about 96 per cent of successful takes and which showed but 2 per cent of spontaneous reactions. The apparatus and the technique employed are described. The effect many times is marked and immediate. The result is a coagulation necrosis and rapid solution of the cells seems to occur at times. In one series of mice 96 per cent survived in adequately controlled experiments. **B. Upon A Transplantable Fowl Sarcoma.**—SCHERESCHEWSKY and ANDERVONT (*Pub. Health Reps.*, 1928, 43, 940) worked with the Rous fowl sarcoma. The results were favorable but less so than with mouse sarcoma. The writers believe the method deserves much more study before its value is determined but consider that it may have important clinical application.

A Unit for Scarlet Fever Streptococcus Antitoxin.—DYER (*Pub. Health Reps.*, 1928, 43, 1659) reviews previous attempts at standardization of scarlet fever streptococcus antitoxin and proposes as a unit "ten times the smallest amount of scarlet fever streptococcus antitoxin necessary to neutralize one test dose of toxin." Protocols illustrating the use of the unit are given. The unit was designed to be of such value that the dose of the antitoxin used clinically would approximate the clinical dose of diphtheria antitoxin when each was expressed in terms of the respective unit.

The Properties of the Bactericidal Substance in Milk.—JONES (*J. Exper. Med.*, 1928, 47, 877) studied certain of the properties of the

bacterial agent in milk. He states that the substance is present in the colostrum and milk of the first few days of lactation as well as later. Its concentration varies in the secretion from various quarters of the same cow. Its activity is diminished by heat and cannot be restored again by the addition of active milk. The principle is present in whey and readily passes through the coarsest Berkefeld filter although a considerable portion is retained by N candles. The finest filter (W) completely retains it. It is adsorbed by animal charcoal but not by kaolin, kieselguhr, or bolus alba. It can be desiccated and its presence has been demonstrated in one brand of dried milk.

An Epidemic of Rheumatism at a Cardiac Camp.—HILLER and GRAEF (*Am. Heart J.*, 1928, 3, 271) report studies on 10 cases of rheumatism, 1 of chorea and 1 of acute tonsillitis occurring within a short period in a group of children at a cardiac camp. Unusually inclement weather coincided fairly well with the incidence of the cases. Although the weather undoubtedly played a part in their incidence, the authors feel that communicability was also a factor.

The Incidence of Clinical Diphtheria among Family Contacts Subsequent to the Discovery of Carriers.—In 1925 DOULL and LARA (*Am. J. Hyg.*, 1925, 5, 508) published a report on the frequency of clinical diphtheria in families in which carriers of diphtheria bacilli had been previously found. These data included 1044 carriers among white school children in Baltimore. DOULL, STOKES and MCGINNES (*J. Prev. Med.*, 1928, 2, 191) studied the incidence of the disease subsequent to the discovery of carriers and reached the following conclusions: (1) That the family contacts of carriers of diphtheria bacilli are exposed, within the *first* month after discovery, to a risk of clinical diphtheria measurably greater than that of a control population living in the same neighborhood, and otherwise considered comparable, but consisting of family contacts of school children cultured and found negative. This is precisely as would be expected from what is known of the epidemiology of the disease. The incidence among family contacts of carriers during this period, is, however, only about one-tenth that of those in similar association with recognized clinical cases. (2) Family contacts of carriers of virulent bacilli seem to suffer a higher risk of attack than do those associated with carriers of bacilli of the so-called "avirulent" type, but there is some doubt whether the proof of this is statistically adequate. Nevertheless, diphtheria incidence in the latter group is, in turn, significantly higher than among the control families. This strongly suggests that those who harbor diphtheria bacilli classified as avirulent according to the usual tests may be of some importance in the spread of the disease. The brief period of increased incidence in the families of carriers is followed by a compensatory period of at least two months' duration in which the attack rate falls below that of the control group. This may be due to a lessened exposure due to a considerable proportion of the carriers gaining immunity to the carrier state, or to immunity acquired by other members of these families through contact with the carrier, or possibly to a combination of both these factors.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 17, 1928.

Some Studies of the Pyloric Sphincter.—J. EARL THOMAS (from the Department of Physiology of the Jefferson Medical College). This report comprises a study of the action of epinephrin on the pyloric sphincter *in situ* and of epinephrin, pilocarpin, atropin, and barium chlorid on the excised pyloric sphincter, of dogs, cats and rabbits.

Graphic records of changes in the tonus of the pyloric sphincter in operated animals under ether anesthesia were obtained by means of a manometer measuring the pressure necessary to force a stream of air of constant volume through a flexible tube lying in the pyloric canal. The stream of air was automatically kept constant by means of a mechanism operating on the principle of a pressure-reducing valve.

Studies of the excised pyloric sphincter have not given satisfactory results in the past due to the failure of the sphincter to manifest a reasonable degree of irritability after excision. This difficulty was obviated by the use of a closed bath in which an oxygen pressure of one atmosphere could be maintained and by regulation of the pH of the bath between 7.6 and 7.8. Deterioration of the tissue after excision was avoided by keeping it in an oxygenated solution at about zero degrees centigrade while dissections were being made. Locke's solution without dextrose was used for the bath.

The primary action of epinephrin on the pyloric sphincter *in situ* may be to cause either increase or decrease of tonus, the former when the muscle is relaxed and the latter when it is contracted. However, increase of tonus in the cat and decrease of tonus in the rabbit were produced but rarely. Large doses of epinephrin had a tendency to cause contraction of the sphincter in the dog and rabbit. Relaxation occurred in the rabbit only with minimal doses given when the tonus of the sphincter was high. Epinephrin generally inhibited the rhythmic contractions in all of the animals.

Epinephrin caused slight contraction followed by more pronounced relaxation of the excised pyloric sphincter of the dog, slight relaxation in the cat, and pronounced contraction in the rabbit sphincters. The results are in accord with the reactions most commonly seen under average conditions in the sphincters *in situ* of the same species. Changes in the tonus of the muscle did not affect the reactions of the excised sphincters, except in degree.

A secondary increase in tonus and augmentation of rhythmic contractions followed the primary effect of epinephrin in the sphincters *in situ* but not in the excised sphincters. It was therefore regarded as an indirect effect in the operated animals not indicative of a direct stimulating action of epinephrin on the pyloric motor mechanism.

The results with epinephrin are interpreted as indicative of a slight

preponderance of inhibitory over motor components in the thoracolumbar sympathetic innervation governing the tonus of the pyloric sphincter in the dog and cat and marked preponderance of motor over inhibitory components in the rabbit. The sympathetic innervation governing the rhythmic contractions is apparently mainly inhibitory in all three species.

The results with pilocarpin and atropin were for the most part a confirmation of previous observations. Pilocarpin caused a moderate increase of tonus and initiated or augmented rhythmic contractions. Atropin caused cessation of rhythmic contractions and slight loss of tonus and manifested its usual antagonism for pilocarpin. Barium chlorid caused marked increase of tonus and augmentation of rhythmic contractions. No species differences were apparent in the reactions to these drugs.

Morphin was sometimes used to supplement the ether anesthesia in prolonged experiments in operated animals, and whenever administered, it increased the tonus and rhythmic activity of the sphincter to a greater extent than either pilocarpin or epinephrin.

The Glass Electrode.—WILLIAM C. STADIE and EFFIE ROSS HAWES (from the Department of Research Medicine, University of Pennsylvania). The glass electrode was found to give satisfactory measurements of the pH of phosphate solutions to ± 0.01 pH units. A modification of the electrode vessel was devised which facilitated the measurement of the pH of CO_2 containing solutions without loss of CO_2 and which would therefore be adaptable to serum and blood. The apparatus was further simplified by the addition of a projecting microscope to project the image of the indicating electrometer needle. The amount of necessary shielding was reduced to a convenient amount and a simple electrically controlled switch introduced.

The Excretion of Morphine.—W. A. WOLFF, C. RIEGEL, E. G. FRY (from the Laboratory of Pharmacology of the University of Pennsylvania). The problem of the excretion of morphine in relation to the development of tolerance has been restudied with the aid of a new method for estimating morphin in biologic material, in which certain errors inherent in older methods are avoided (*J. Biol. Chem.*, 1928, 80, 379). The accuracy of the method when applied to urine is very satisfactory; less so for feces, the results being consistently high. Hence the fecal excretion is, in all probability, represented as too great.

Normal dogs, each given a single dose of morphin the size of which varied between 25 mg. and 200 mg. per kilo body weight, eliminated 11 to 23 per cent in the urine; feces contained from traces up to 7 per cent. The percentage elimination is of the same order regardless of size of dose. Similar differences in urinary elimination are encountered in litter mates or in the same dog when he is injected more than once.

During the development of tolerance by repeated daily injections the percentage of morphin eliminated did not change either consistently or significantly. A series of four dogs tolerant to doses ranging from 25 mg. to 60 mg., which had been kept on a morphin régime for periods varying from seven to five hundred and forty-three days, gave 10 to 14 per cent elimination in urine; 2 to 6 per cent in feces. Hence tolerance

is not characterized by significant increase in capacity to destroy morphin as was held by Faust (*Arch. f. exper. Path. u. Pharm.*, 1900, 44, 217) and later by Teruuchi and Kai (*J. Pharm. and Exper. Ther.*, 1927, 31, 177).

A few data on excretion by the human addict roughly parallel those for tolerant dogs.

Gastric Motility in Vitamin-B Deficiency.—W. B. ROSE, C. J. STUCKY and G. R. COWGILL. In 1917 Osborne and Mendel observed that anorexia was a prominent symptom of vitamin-B deficiency in rats. Likewise in 1920 Karr noted that dogs lose their appetite when deprived of vitamin-B. Cowgill and others (1926) investigated the motor function of the stomach in vitamin-B deficient dogs and reported that in the advanced stages of this deficiency, when anorexia was associated with nervous and muscular symptoms there was gastric atony.

However, this assertion of the occurrence of gastric atony in the presence of neuromuscular symptoms of vitamin-B deficiency, brought forth the criticism by an eminent investigator that the gastric atony observed, was in all probability due to the fact that the animal was moribund. This interpretation was strengthened by the work of Erma Smith (1927) who reported that tracings of gastric motility of vitamin-B deficient dogs were indistinguishable from those obtained in normal controls.

In view of this conflicting evidence, a study of the hunger contractions in B-avitaminotic dogs was undertaken with certain definite modifications in procedure. Thus a series of control animals were employed, each of which received the same amount of food and water daily that was consumed by a corresponding deficient dog. In addition the controls were given their full quota of vitamin B daily regardless of their food and water intake. In this way an attempt was made to duplicate, insofar as possible, nutritive changes resulting from vitamin-B deficiency, leaving a lack of vitamin B as the only known variable. Parallel blood studies were made on both control and deficient animals throughout the experiment. A technique was developed which made it convenient to record hunger contractions, continuously over a period of twenty-four hours or longer.

In general the results point to the fact that there is a distinct decrease in the motor power of the stomach in vitamin-B deficiency. In two animals gastric atony was recorded for periods of over fifty and one hundred hours respectively. This atony occurred a week or more before neuromuscular symptoms developed. Liberal administration of material rich in vitamin B resulted in a return of the normal gastric tonus, rhythm and hunger contractions.

Although none of the control animals developed gastric atony, they manifested a definite decrease in gastric motility. However, one control dog continued to show normal vigorous hunger contractions throughout. This is of particular interest and will be referred to again.

The decrease in gastric motility observed in the present study cannot be attributed to hyperglycemia, because the blood-sugar level remained well within the normal range in all cases throughout these experiments.

On the other hand our data seem to indicate that vitamin-B deficiency

is associated with a variable increase in blood concentration. It seemed that the depression in gastric motility was related to some extent at least to changes in blood concentration. The same appeared to hold true for the food- and water-control dogs. The control animal which did not manifest any decrease in gastric motility was the only one in which the blood concentration did not vary throughout.

Normal dogs, fed a diet complete in every known respect, including an adequate supply of vitamin B, were deprived of water. When the hemoglobin had increased approximately 20 per cent, gastric atony prevailed in all cases. Administration of fluids was soon followed by a decrease in blood concentration and a return of the normal hunger contractions.

In conclusion it may be stated that vitamin-B deficiency is associated with a definite decrease in gastric motility, and that one contributing factor has been demonstrated.

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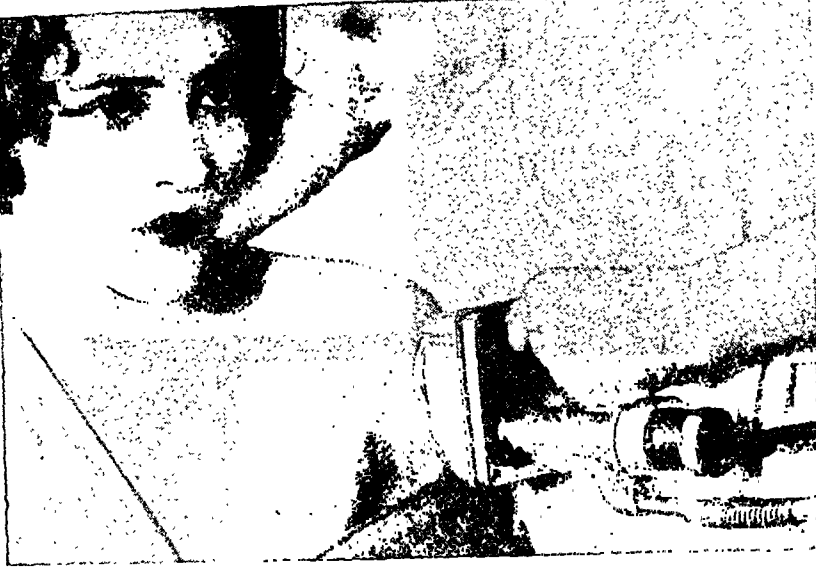
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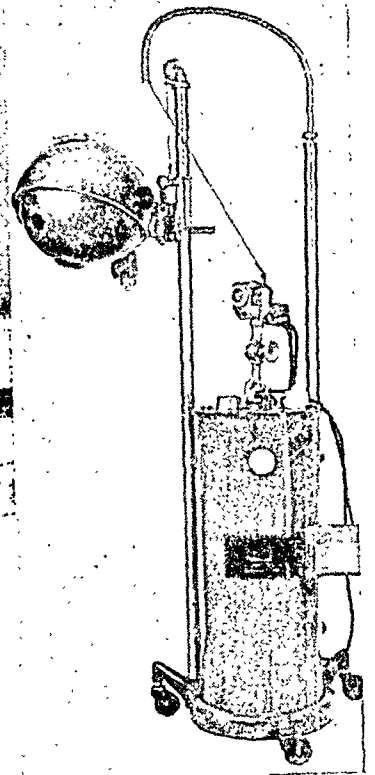
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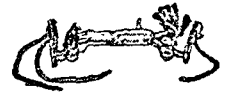
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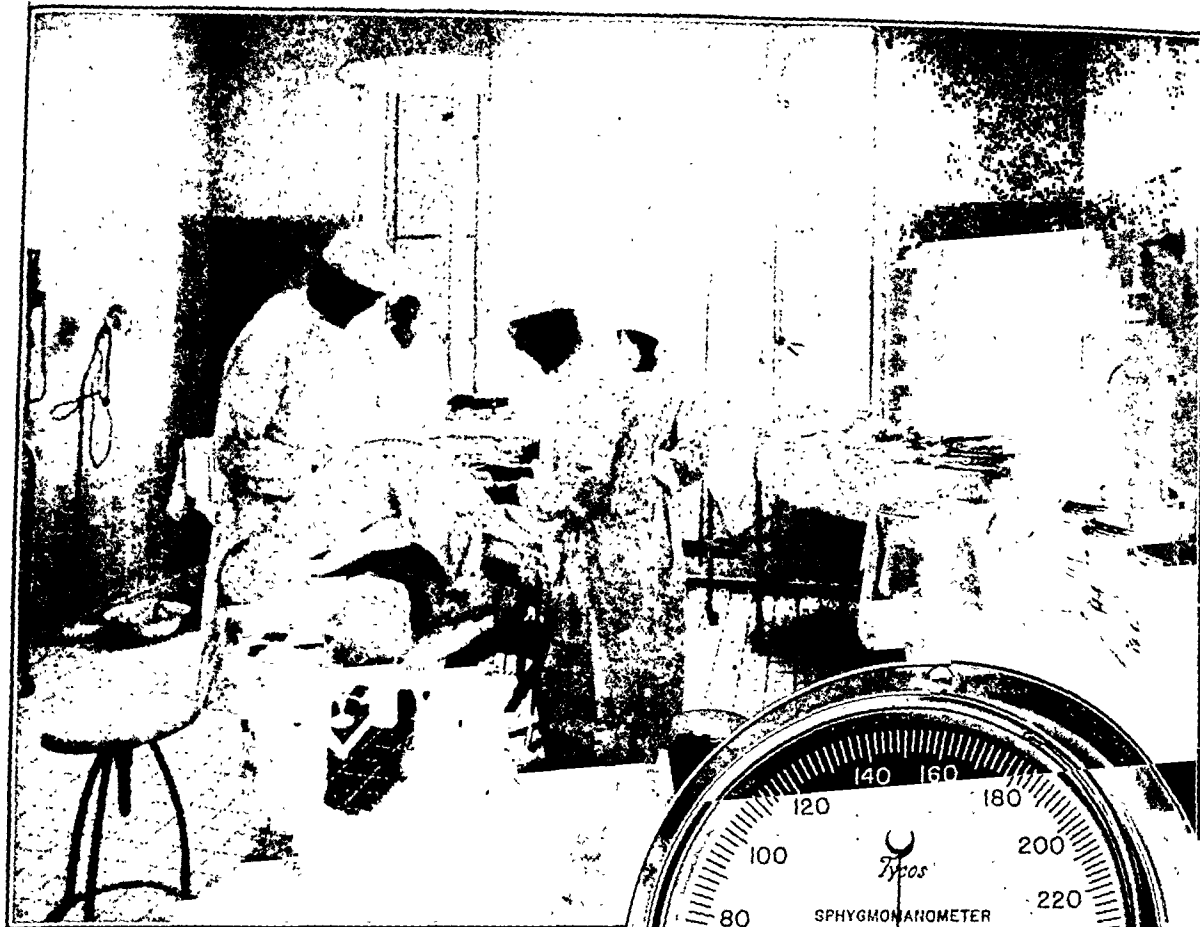
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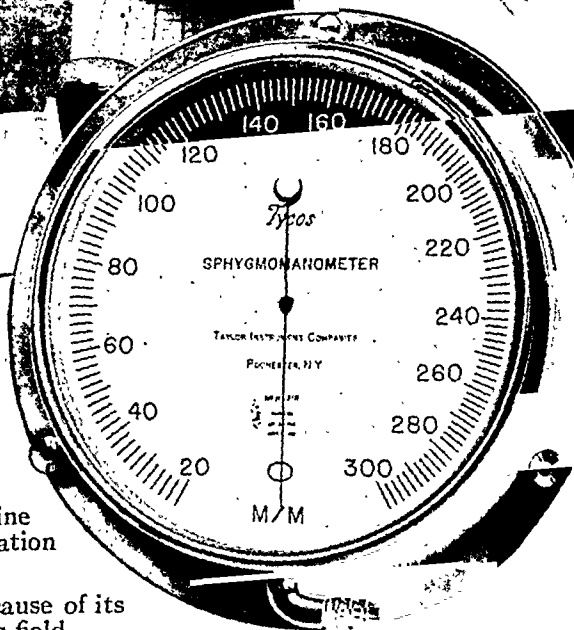
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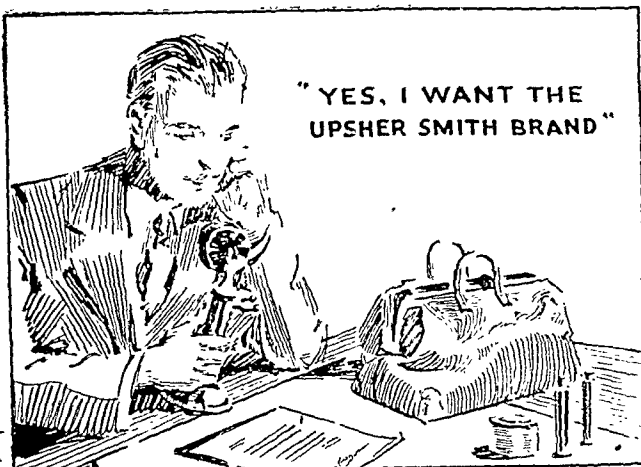
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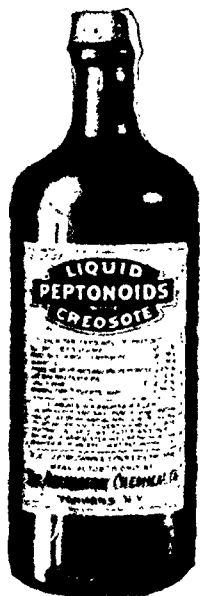
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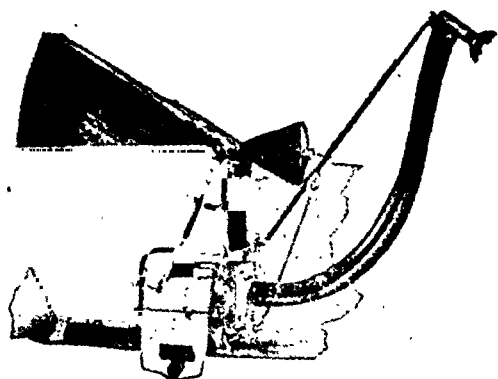
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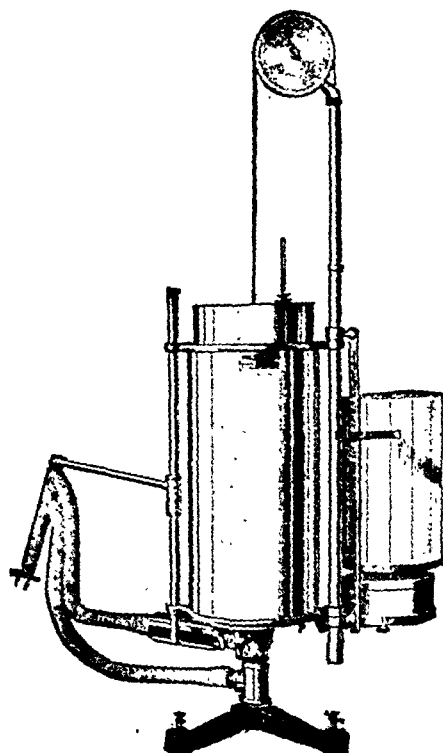
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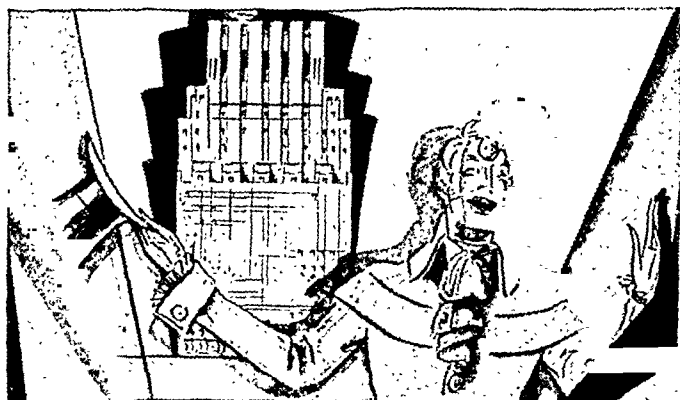
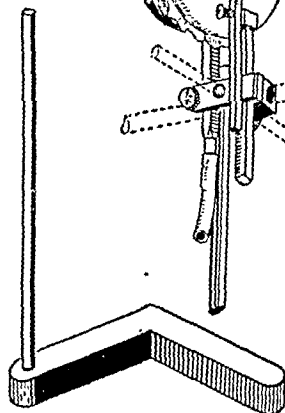
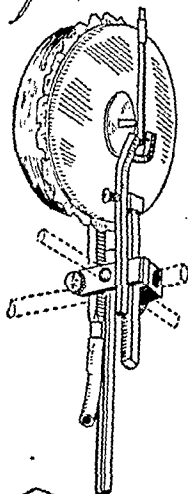
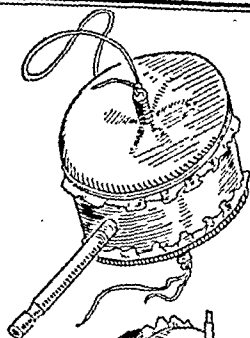
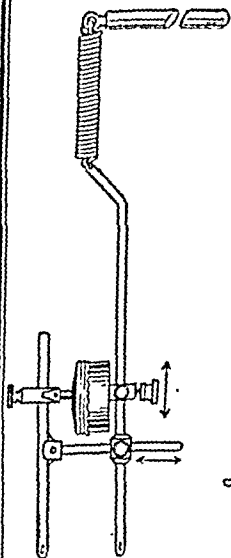
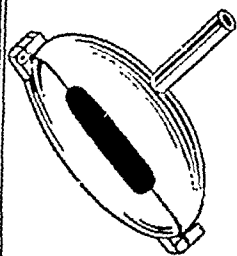
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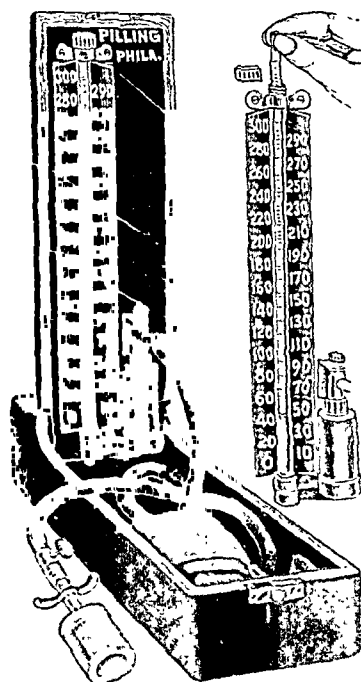
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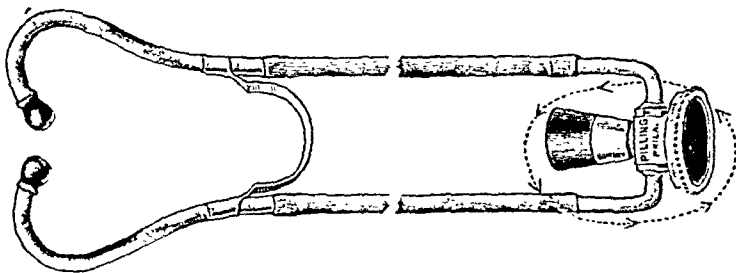
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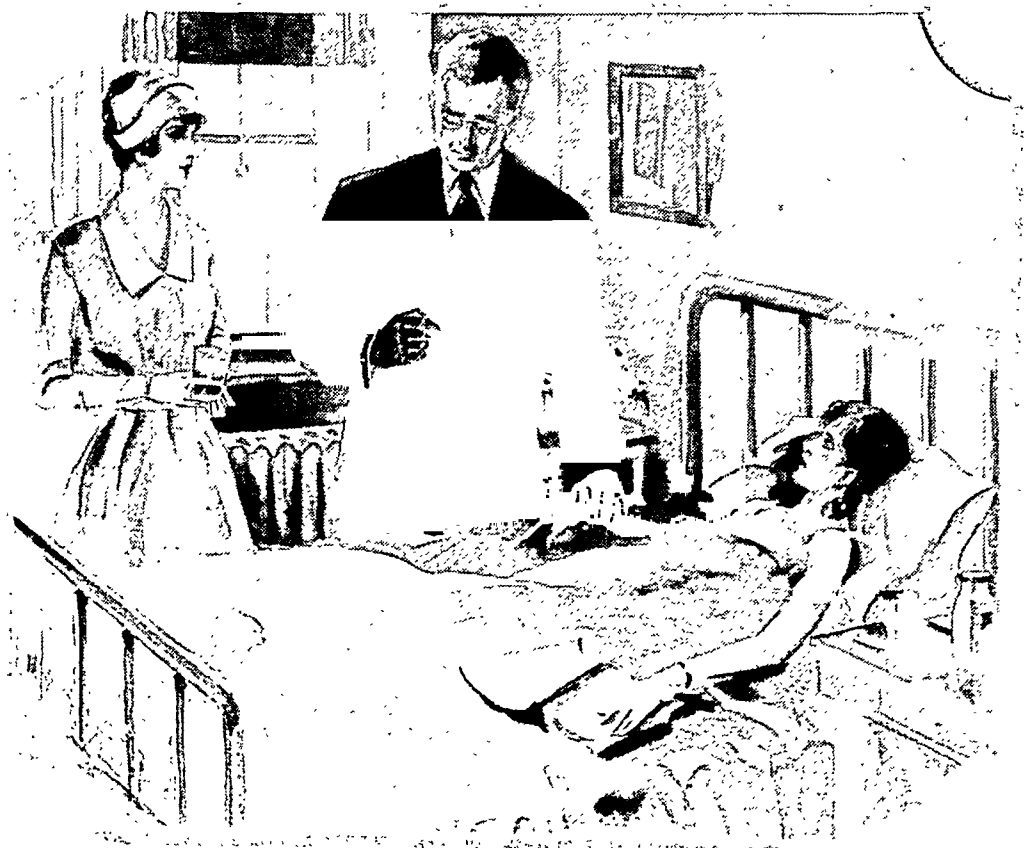
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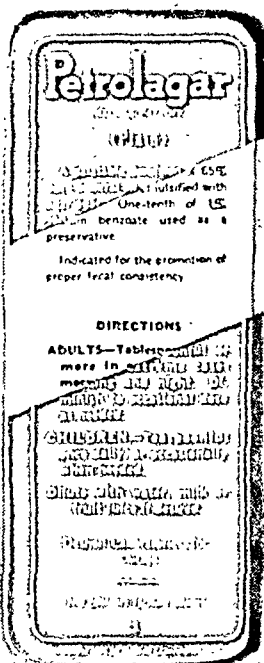
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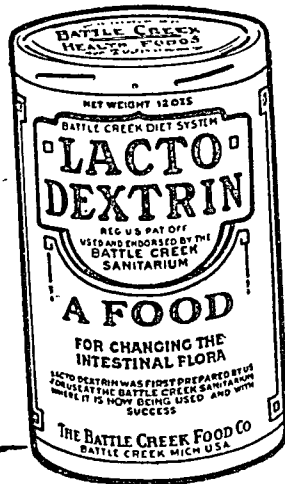
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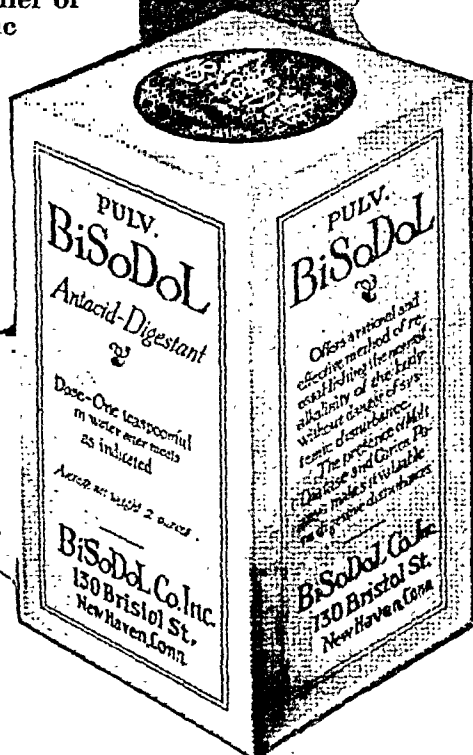
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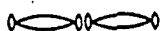
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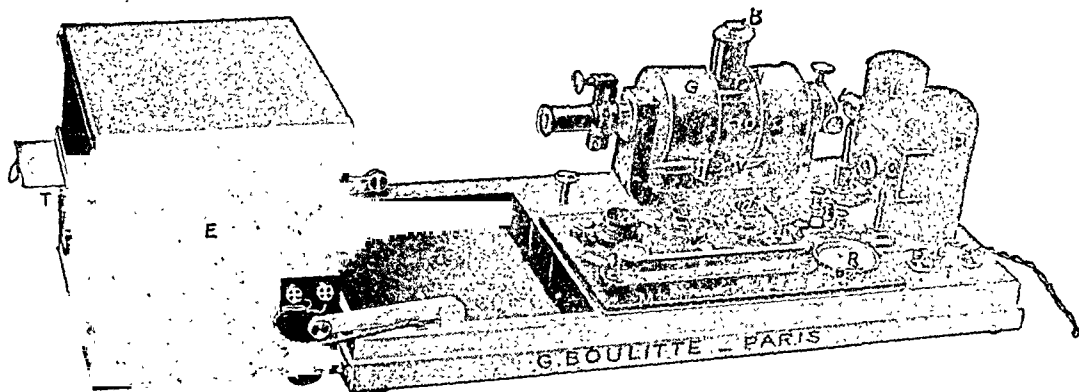
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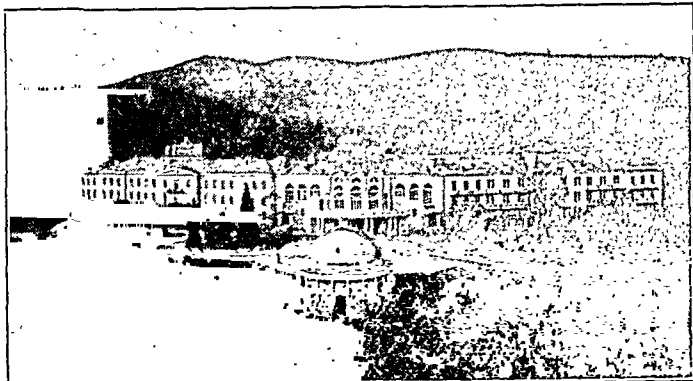
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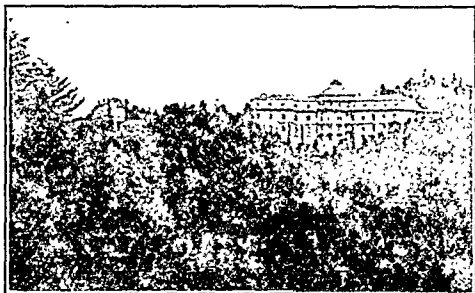
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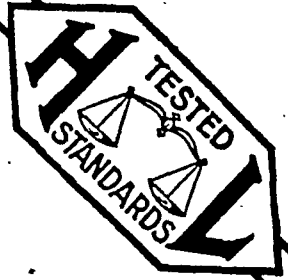
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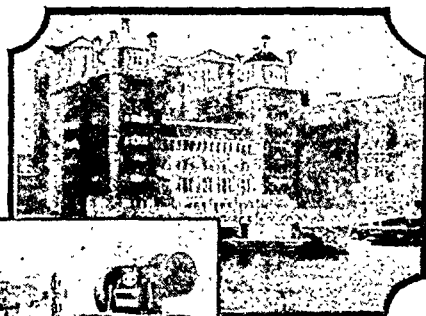
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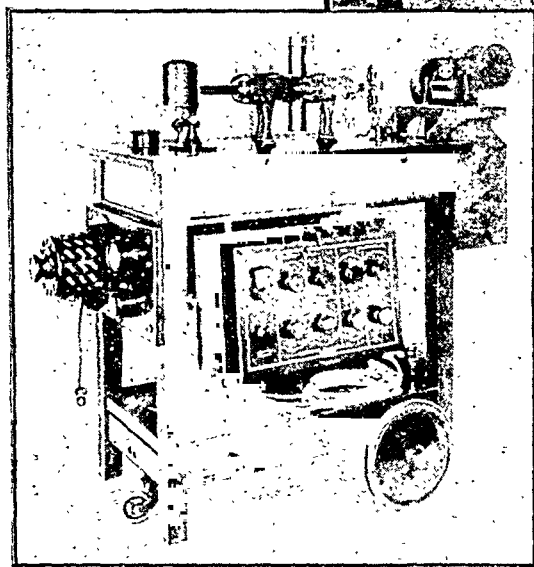
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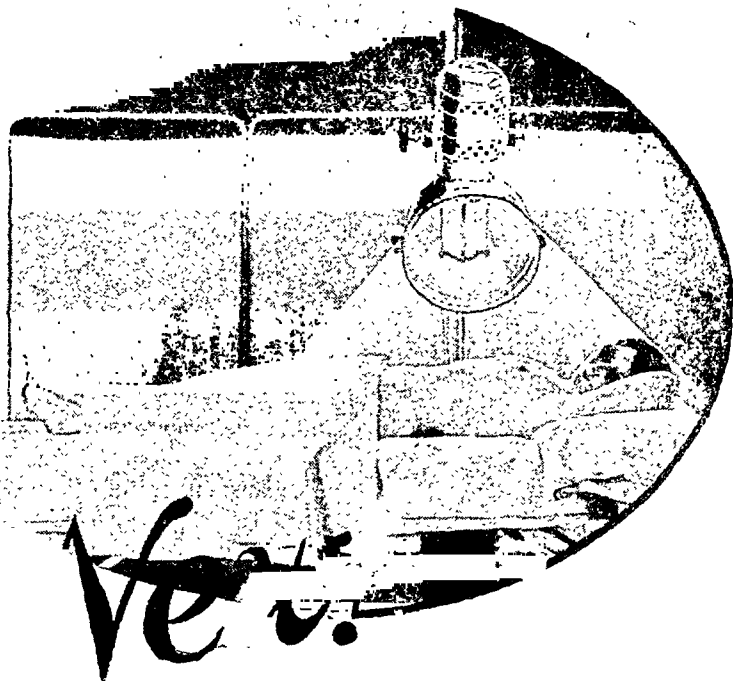
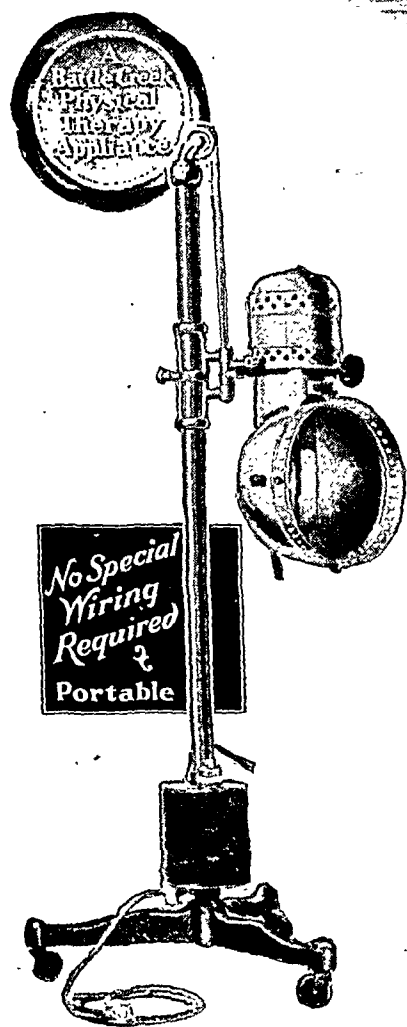
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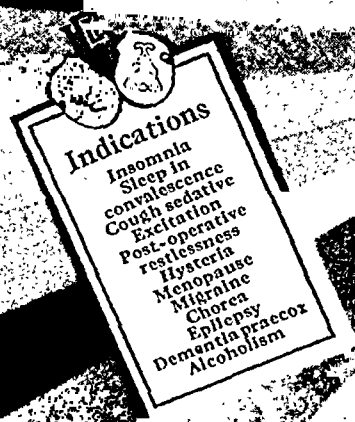
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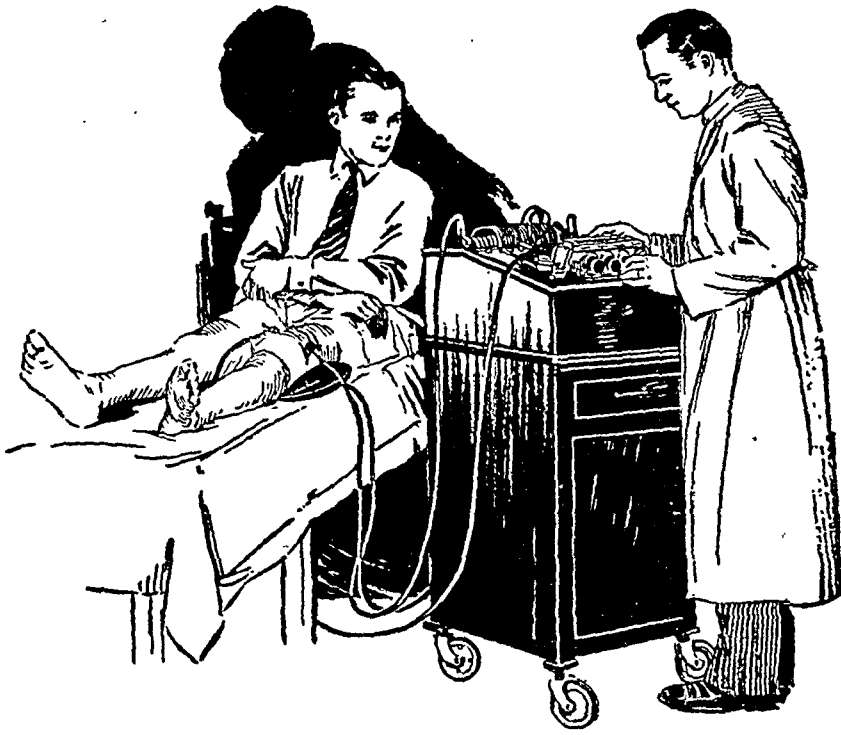
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THE
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APRIL, 1929

ORIGINAL ARTICLES.

THE RELATION OF CANCER TO OLD AGE.*

BY JAMES EWING, M.D.,

PATHOLOGIST TO MEMORIAL HOSPITAL, NEW YORK.

THAT cancer† is a disease of old age is one of the cherished tenets of clinical medicine. Contrasted with the comparative rarity of the disease in youth, its common occurrence after middle life and great frequency in advanced ages, have led many to conclude that cancer may almost be considered a function of senescence and a somewhat natural outcome of senile changes in the organs. Yet, a review of the literature fails to reveal any very critical investigation of the basis of this common tenet, most observers being content to record statistics showing the age periods when cancer is most frequent. When, however, one begins to consider the real significance of the supposed relation of old age to cancer, one immediately encounters numerous problems of considerable complexity. What is meant by "old age?" Is the incidence of cancer in old subjects an accident, or is it the result of factors essentially connected with the aging process? At what period of life may one consider that old age is established and is the period always the same in different races and individuals? What is meant by "cancer?" Is it always essentially the same disease with a uniform etiology, or does this term cover a multitude of diseases with varying causation? How shall we dispose of the numerous malignant tumors of infancy and youth? Are there any tumors peculiar to advanced ages, and are there any peculiarities of ordinary tumors which may be attributed solely to the age factor? These are some of the inquiries which must be

* Contributed to Old Age Fortnight of the New York Academy of Medicine, October 1928.

† The term cancer is here used to include both sarcoma and carcinoma.

VOL. 177, NO. 4.—APRIL, 1929

answered before one can determine whether there is any real clinical significance in the relation of cancer to the age factor.

It is first necessary to determine the age incidence of the different forms of cancer. For this purpose there are available adequate statistical studies of considerable scope and reliability.

In 1905, Lazarus-Barlow made an elaborate study of the age incidence of cancer in 4659 female and 2073 male patients dying from cancer in the Middlesex Hospital, London. His table gives a valuable index showing the age incidence of the various forms of cancer in both sexes, as patients apply at a general hospital. These figures have not been considered in relation to the total population living at the different periods. They reflect the general clinical experience that cancer occurs most frequently between fifty and sixty years. (Table I.)

TABLE I.—TABLE SHOWING THE VARIOUS SITES OF PRIMARY CANCER ARRANGED IN ORDER OF THE COMPUTED AGES AT WHICH THEY ARE LIABLE TO OCCUR.

(Compiled from 2073 Male and 4659 Female Cases in the Records of the Middlesex Hospital.)

Age.	Males.				Females.			
	Site of growth.	I.	II.	III.	Site of growth.	I.	II.	III.
45 to 49	Breast. . . .	52.263	42	46.8	Uterus. . . .	46.707	47	46.8
	Scrotum . . .	47.417	47	47.2	Vagina	49.725	45	47.3
					Breast	51.434	47	49.2
					Tongue	52.171	47	49.5
50 to 54	Penis	52.290	52	52.1				
	Stomach . . .	52.339	52	52.2	Esophagus . . .	49.700	52	50.8
	Larynx	55.954	50	52.9	Rectum	51.437	52	51.7
	Tongue	54.587	52	53.4	Larynx	53.600	52	52.8
	Colon	55.372	52	53.7	Pancreas	54.414	52	53.2
55 to 59	Bladder A . .	59.920	52	55.8	Colon	53.276	57	55.1
	Esophagus . .	55.666	57	56.3	Vulva	55.682	57	56.3
	Liver	53.836	62	57.8	Stomach	52.042	62	56.8
	Rectum	54.086	62	57.9	Mouth (excluding lip and tongue).	56.727	57	56.9
	Mouth (excluding lip and tongue)	55.314	62	58.5	Bladder	59.478	57	58.2
	Pancreas . . .	57.200	60	58.6	Liver	55.414	62	58.6
					Skin	55.946	62	58.9
					Lip	60.714	52	59.7
Above 60	Rodent cancer .	58.261	62	60.1				
	Lip	58.668	62	60.3				
	Skin	60.233	62	61.1	Rodent cancer .	55.347	67	63.1
	Anus	61.800	62	61.9	Anus	66.857	62	64.4
	Bladder B . .	59.920	67	63.4				
	Prostate . . .	67.400	72	69.7				

Column I, mean age of all cases. Column II, mean age of quinquennial period in which maximum number of cases occurred. Column III, average I and II.

It is important that in this series about 80 per cent of the cases were cancers of the uterus and breast. In males, cancer of the breast and scrotum occurred early; cancer of the liver, rectum, mouth and pancreas occurred very late. In females the order is much the same, but the early occurrence of cancer of uterus, vagina, breast and tongue is noteworthy. In both sexes, cancer of the generative system affords the early cases, cancer of the skin the late cases, and cancer of the alimentary tract gives the intermediate group. A period of twenty-three years separates the acme of early and the late cases.

Many other similar studies have yielded much the same results, so that it must be regarded as fully proven that the greatest number of cancer cases occur at and shortly after middle life, and between the ages of fifty and sixty years. This fact becomes more significant when it is considered in relation to the number of persons living at this decade as compared with other life periods. The U. S. Census Report on Cancer, 1914, shows that in the Registration area there were about 12,000,000 persons living at each decade from ten to thirty years; 9,200,000 between thirty and forty; 7,000,000 between forty and fifty, and only 6,000,000 between fifty and sixty, and thereafter about a 50 per cent decrease in each succeeding decade. So it appears that the greatest number of cancer deaths occur at a time when the total population living at that period is considerably reduced.

The Metropolitan Life Insurance Company has made a very exhaustive and valuable analysis of the cancer deaths among its policyholders, covering the twelve-year period, 1911 to 1922. They found a slight increase and upward trend, especially marked after fifty-five years, while between thirty-five and fifty-five years the trend was downward. The gravity of the cancer situation is thus concentrated on the older ages, not only from the standpoint of maximum incidence, but from that of increasing mortality. Two per cent of all the cancer deaths were of persons under twenty-five years of age, due to the occurrence of sarcomas. The deaths from cancer of the uterus, rectum and anus, were excessively high among colored women. The upward trend of the death rate from cancer of the intestinal tract was more pronounced than for any other group, and was most marked after fifty-five years. Breast cancer caused 13.8 per cent of the deaths among white females, the rate was even higher among colored females, and it was increasing for both races. The trend of the death rate for buccal cancer was downward between 1911 and 1922, except for colored males. An interesting fact was the higher death rate from cancer of the skin among whites, as compared to negroes. The death rate from cancer of the skin gave 4.1 per cent of all cancer deaths among white males, 2.1 per cent for colored males, 1.8 per cent for white females, and 0.9 per cent for colored females.

The great value of this study lies in the separate consideration of different forms of cancer in different races, since the results give a clue to the action of specific factors entering into causation.

The foregoing studies show that the greatest number of cancer cases occur just after middle life; but they do not show whether there is an increasing liability to cancer from the beginning to the end of life, and especially in the advanced age periods. Two important studies refer to this interesting inquiry. In 1905, Bashford published an analysis of 3576 cases collected from the London Hospitals and confirmed by pathologic diagnosis, and considered the age incidence of the cases with the total population living at the various periods. (Table II.)

He found that there is a progressive increase in the liability to nearly all forms of cancer at each age period up to eighty-five years, after which there was a slight, but unimportant decline. The occurrence of a very high proportion of cancers of skin, tongue in males and of breast in females is worthy of note. Only tumors of the brain showed a marked decrease after seventy-five years. This table also shows the well-known fact that the period between five and ten years is marked by a notable incidence of tumors of the brain, kidney and adrenal. The lowest incidence of the disease, as a whole, occurs about the tenth year, after which there is a continuous increase in the total number of cases and in the liability. The same conclusions must be drawn from the U. S. Census Report of 1914. (Table III.)

This table shows a continuous increase in the liability to cancer at all age periods up to eighty-five years, with a slight decrease beyond that period. The increase is remarkably uniform for all forms of cancer except tumors of the brain.

Somewhat divergent results were obtained by Weller, but in a selected material coming to a general hospital. Weller determined the age incidence of 1106 cases of cancer diagnosed in the Ann Arbor Laboratory. There was a steady increase in the number of cases up to the sixtieth year, with a progressive decrease thereafter. Compared with the population living at the different periods, the greatest incidence of cancer was, for females, between fifty-eight and sixty-two years, for males between sixty-eight and seventy-two years, followed by a slow decline up to eighty-two years. The earlier incidence of cancer of the uterus and breast accounted for the discrepancy between the sexes.

At the Mohonk Conference, Dublin presented an important study of the chances of dying of cancer at the different age periods, based upon an analysis of 125,000 cancer deaths among the policyholders of the Metropolitan Life Insurance Company in the years 1910, 1922 and 1924. In 1910, among 100,000 persons living at the age of ten years, there would be 5874 cancer deaths up to the

TABLE II.—ENGLAND AND WALES.
Deaths per 1,000,000 Living at Each of the Age Periods Given. Average 1901 to 1904, Illustrating the Different Age Periods at which Cancer of Certain Organs Begins to Increase Rapidly in Frequency.

	Under 5 years.	5 to 10 years.	10 to 15 years.	15 to 20 years.	20 to 25 years.	25 to 35 years.	35 to 45 years.	45 to 55 years.	55 to 65 years.	65 to 75 years.	75 to 85 years.	85 and upward.
MALES.												
Skin	0.79	0.28	0.46	0.61	1.00	2.37	10.53	36.34	103.39	278.49	734.23	1650.20
Stomach	0.15	0.15	2.33	15.08	89.69	325.62	875.64	1530.94	1490.714	736.45
Rectum	0.13	...	0.46	0.91	4.83	10.94	35.90	142.54	393.57	718.54	826.19	668.26
Tongue	0.15	0.15	...	1.58	21.82	114.10	224.59	278.73	305.56	1772.94
Brain	3.30	3.38	2.49	2.90	3.33	6.31	10.66	16.50	20.25	13.34	2.97	13.64
Shoulder	0.26	0.14	0.29	0.61	0.83	0.89	1.01	2.11	4.05	8.72	14.83	13.64
Kidney and adrenal . . .	7.93	1.69	0.73	0.46	1.17	1.77	5.71	16.68	33.47	45.65	54.88	13.64
FEMALES.												
Skin	0.53	0.14	0.15	0.15	0.30	1.06	4.39	15.29	32.65	97.87	267.48	553.62
Stomach	0.13	...	0.15	0.15	1.04	12.38	79.27	278.78	678.29	1195.33	1255.77	834.43
Rectum	1.49	2.23	11.05	36.31	122.80	271.13	441.44	552.15	312.91
Uterus	0.26	0.45	3.30	61.99	337.25	746.34	967.16	1012.29	910.94	730.13
Breast	0.15	0.15	0.74	20.16	168.86	460.28	699.11	966.42	1407.23	3013.88
Tongue	0.13	0.15	2.21	3.68	7.64	17.98	42.18	49.41	24.07
Brain	1.32	2.10	1.76	1.64	2.97	4.33	9.85	11.55	13.49	10.65	6.45	8.02
Shoulder	0.28	0.29	0.45	0.30	0.71	0.95	1.30	4.02	4.91	7.52	24.07
Kidney and adrenal . . .	8.16	1.54	0.59	0.60	0.59	1.33	5.70	16.92	28.39	43.41	54.79	24.07

TABLE III.—PROPORTION OF CANCER DEATHS TO TOTAL POPULATION LIVING AT EACH AGE PERIOD,
U. S. CENSUS REPORT, 1914.

Death Rate per 100,000 Population by Sex and in the Age Group Specified.

	Under 25 years.	25 to 34 years.	35 to 39 years.	40 to 44 years.	45 to 49 years.	50 to 54 years.	55 to 59 years.	60 to 64 years.	65 to 69 years.	70 to 74 years.	75 to 79 years.	80 to 84 years.	85 years and over.
Male	2.8	8.7	21.5	43.0	78.9	140.9	237.7	339.8	467.0	627.4	684.2	826.4	824.3
Female	2.7	19.6	64.7	118.7	184.4	266.5	381.1	449.4	566.6	717.1	845.5	946.2	916.7
Total	5.5	28.3	86.2	161.7	263.3	407.4	618.8	789.2	1033.6	1344.5	1529.7	1772.6	1741.0

end of life, but in 1924, the calculated deaths had increased to 8652, (47.3 per cent), owing to the reduction of deaths from other causes. Dublin comments on the alarming significance of this conclusion, since the reduction of deaths from other causes is bound to continue and more and more people will reach the cancer age and eventually die of this disease. He thinks that the attitude of the medical and public health professions toward cancer should be revised and greatly increased efforts made to meet the problem.

Very similar conclusions were reached by Schereschewsky from a study of the U. S. Census Reports.

It is necessary to point out a possible misinterpretation of these statistical studies. They do not show that there has been any increased tendency toward cancer in any individuals at any age. They merely show that people are living longer, so that the lapse of time permits the expression of whatever tendency to cancer they may possess. The liability of exposure to exciting factors of some cancers, as of skin and lung, may have increased in the past twenty-five years, but these studies do not prove this to be a fact.

A comparison between the white and colored races appears in the study of Pearl and Bacon. They analyzed 6670 autopsied subjects at the Johns Hopkins Hospital, among which there were 816 cases of malignant tumors, or 12.2 per cent. This percentage is somewhat higher than that of the general population. Their main conclusions were that cancer occurs much more frequently in whites than in negroes, and slightly more often in females than in males. The highest proportion of cancer deaths, compared with total deaths occurred between the ages of fifty-five and sixty-five years, except for females, with whom the mortality from uterine cancer seems to have advanced the main period of deaths about five years. They do not consider the relation of total cancer deaths to total population living in the different age periods, but quote Dublin's observations which show that there is an increasing chance of death from cancer up to the end of life.

Both the above types of statistical studies suffer from some inaccuracies. In the census material, large numbers are involved, but the diagnoses are uncertain, while in the hospital material in which the diagnosis is certain the cases are more or less selected. The fact that the results from both classes of studies are identical seems to assure the general reliability of each.

Some interesting details regarding the cancers of old age are furnished by the report of Roussy, LeRoux and Vermes of 1000 autopsies occurring in a home for the aged. Among these autopsies there were 77 cases of cancer, 32 in males, 45 in females, 39 clinically recognized, 38 found at autopsy. The distribution was as follows:

TABLE IV.—DISTRIBUTION OF CANCER OF THE AGED.

Decades, years.	No. cases.	Organ.	Cases.	Organ.	Cases.
50 to 59 . .	2	Stomach	27	Lung	2
60 to 69 . .	14	Uterus	8	Gall bladder . .	2
70 to 79 . .	32	Skin	5	Bladder	2
80 to 89 . .	19	Colon	5	Liver	2
90 to 99 . .	1	Kidney	5	Thyroid	2
	—	Pancreas	5	Breast	1
	68	Rectum	3	Tongue	1
Unknown . .	9	Esophagus	3	Unknown	4

There was only one sarcoma, type not stated.

The authors emphasize the important part played by infection as the cause of death in these cases. Death was attributed to cancer cachexia in 24 cases, to cancer plus infection in 6, and to intercurrent infection in 47. Probably much the same results would be revealed by a study of cancer deaths at other ages, but they suggest that in old subjects the progress of cancer is somewhat less rapid than at other ages, and that intercurrent infection plays a larger part in the disease in old persons than in younger subjects.

The high incidence of cancer in old age is not limited to human beings, but probably exists in all species of animals.

Old dogs are especially prone to develop such tumors and it is rare to find an old dog over fifteen years of age which does not exhibit one or more benign or malignant tumors. Goodpasture and Wislocki found tumors in all of 15 old dogs which showed signs of senility such as loss of teeth and cataract. In most of the animals several organs contained tumors. The tumors were adenomas of the liver and adrenal in most cases, adenomas of thyroid, papillary adenomas of gall bladder, stomach, ovary, prostate and pancreas, cystic adenoma of thymus, angiomas of spleen, lipomas and fibromas. Mammary cancer is so common in old bitches that such animals cannot safely be used for the experimental production of mammary cancer.

Cohrs found 77 tumor-bearing domesticated animals among 737 autopsies; and of the 77, the tumors were multiple in 26. He noted the greater frequency of tumors in older animals, and especially their multiple character. In the causation of these tumors he laid greatest importance on the congenital abnormalities in structure and on recurrent chronic irritations.

The foregoing studies seem quite adequate to show these main facts: first, that the greatest incidence of cancer occurs shortly after middle life; second, that there is an increasing liability to cancer practically up to the end of life; and third, that the liability to cancer has increased greatly in the last two decades. However, the real medical significance of these facts remains entirely unexplained. One may accept the economic importance of statistical facts presented without admitting that they prove any essential connection of can-

cer with senility. Automobile accidents, multiplication of grandchildren, and accumulation of wealth all belong especially to old persons, but they have nothing to do with the process of senescence. One must inquire into the reasons for the occurrence of cancer in old persons. This inquiry leads at once into many complicated questions.

What is old age? Is it to be accepted merely from the chronologic side, or is it to be considered from the physiologic standpoint? Now, it is at once apparent that the changes of senescence occur at very different periods in different individuals, since some age rapidly, and others slowly. Moreover, the changes of senility are very prone to affect one organ before another. Unless one limits the observations to very advanced periods, as after seventy years, one will include in the category of senility many persons who show very little, and some who show no definite senile degeneration of the organs. I have often been struck at autopsies on subjects dead of epidermoid carcinoma at very advanced age, with the remarkable preservation of the organs. In these cases the disease had resulted from strictly local factors, not connected with age. It is unsound to assume that every person who dies of cancer at the age of seventy-five has contracted the disease because of senility. This is one of the reasons why crude statistical studies must always fail to yield wholly reliable indications in this field.

Another source of error lies in the fact that the date of death from cancer does not always indicate even the approximate period of the inception of the disease. Much less does it indicate the time of initiation of the process which led to cancer. On this account, many authors have concluded that statistics cannot bring us any nearer to a solution of the biologic problem of cancer, nor establish an essential relation of the disease to old age.

Mertens refers to the considerable number of cases of cancer in young subjects. He notes the occurrence of the changes of senility in the organs of young adults, and he records several cases in which the recognition of the disease came many years, even twenty-five, after the beginning of the process. Thus he is unwilling to admit that any essential connection between cancer and old age has been demonstrated. Freund, Lewin and others reach much the same conclusion.

Particularly important in this connection is the principle of action of the cancerigenic agent, at a distance in time. Aniline cancer of the bladder may develop many years after the exposure to the irritant has ceased. One observes cases of cancer of the skin developing many years after the application of hot tar. Cancer of the lip and of the anus are notably frequent in advanced years, but they probably result from the cumulative action of many forms of irritation spread over many years. The effective exciting factors in cancer are thus very often hidden and their effects postponed for

many years, so that the date of appearance of a cancer may not at all indicate the date of origin of the process. It is very difficult or impossible to estimate how frequently the appearance of cancer is thus delayed, but it seems certain that a long evolution of the cancer process occurs in a high proportion of cases. We must, therefore, conclude that many cancers appear in old age, not because they are the result of any element of senescence, but merely because the lapse of time allows the fruition of processes which have their inception at a much earlier period.

What are the factors in senescence which may tend to produce cancer and how often are they actually found to be the main basis of the disease? Among the conditions found in the bodies of old subjects, there are three which are of obvious importance in this inquiry: (1) atrophy of the parenchyma of organs, often attended with deposit of pigment; (2) replacement fibrosis; (3) arteriosclerosis. It seems probable that the controlling element in all these processes lies in changes in the bloodvessels, both large and small. In each organ the changes produced are characteristic. In the skin there is atrophy of the elastic tissue, thinning, dryness, pigmentation and hyperkeratosis. The atrophy of subcutaneous fat produces wrinkles. In the liver there is simple atrophy with pigmentation, and some replacement fibrosis. All glands of internal secretion show cellular atrophy and fibrosis which are, at times, pronounced. The kidneys are reduced in size, indurated, and usually show some cortical areas of atrophy from narrowing of bloodvessels. All mucous membranes tend to show reduction in glandular tissue and lymphoid stroma. The special sense organs suffer atrophy of the specialized cells and fibrosis. The lymphoid tissues are much reduced in bulk and may exhibit complete atrophy. In the blood-vascular system, there is general reduction of muscle and elastic tissue, causing reduced circulation. The bones contain excess of calcium and are brittle, while the cartilages and joint capsules are often calcified, atrophied and inelastic. The red marrow disappears, except in the vertebræ and flat bones. The blood volume is reduced.

From the physiologic side, all these changes tend to produce lowered functional and metabolic activity.

Many authors have urged the prime importance of arteriosclerosis in the origin of cancer, but extremely few have given any data of real value on this subject. Warner studied 206 cases of cancer and found arteriosclerosis in the affected organ in 105 (51 per cent); fibrosis in 127 (57 per cent). This report is a fair index of the association of cancer with arterial disease in the average material, but arteriosclerosis is probably much more frequent in old subjects. There are a few characteristic forms of cancer in old subjects, which are referable to arteriosclerosis, but this lesion is absent in a large proportion of cases at all ages. Even when present it may not be an important factor in the genesis of cancer.

It is at once evident that none of these conditions, briefly enumerated, give any direct clue to the origin of cancers, and it becomes necessary to analyze the conditions in far greater detail in order to establish a connection between old age and cancer. However, one general factor common to all the above states may be recognized as of importance. Thiersch conceived that in the tissue atrophy of old age the connective tissues offer less resistance to the better surviving epithelial tissue, so that abnormal epithelial proliferation occurs more readily. This theory assumes that there is more atrophy of connective than of epithelial tissue, and it fails to account for the atypical character of the proliferation, but it has generally been accorded considerable importance.

To trace the changes of old age into cancer is a very difficult problem since it involves a knowledge of the very beginnings of cancer in the different organs, and these beginnings have seldom been observed. Here the inquiry must be quite detailed and specific and directed to each particular cancer in each organ. A comprehensive study of this subject cannot be attempted in the scope of this communication, but a brief effort may be made to trace some of the cancers of old age to the conditions essentially belonging to this period of life.

Cancer of the Skin. Pigmented epidermoid cancer of the skin, or malignant lentigo, is a well-known tumor of the skin which is clearly connected with the aging process. It begins in one or more small pigmented spots, which gradually enlarge, coalesce, become heavily pigmented, and after many years begin to show infiltrative growth with marked malignancy. It is not a true melanoma, but an epidermoid carcinoma. It is often associated with general xeroderma pigmentosa. The sclerosis of the derma, and the accumulation of pigment belong to the process of senescence. How they combine to produce cancer is unknown. The process extends over many years, so that the inception cannot be ascribed to old age alone, and there is the further difficulty that very similar pigmented atrophy of the skin resulting in carcinoma occurs in young subjects. Indeed one must admit that the essential process, which consists in a disturbance in the pigment forming function, probably hereditary, has no essential connection with senescence, but merely requires the lapse of time to express its results.

Senile angioma must be regarded as essentially a disease of old age, at least in respect to frequency and number of lesions. It is said that at least 75 per cent of all subjects over sixty years of age present these tumors, sometimes in very large numbers. They are varicosities in the small bloodvessels of the skin and may be referred to gradual atrophy of the elastic tissue.

Rodent Ulcer. Although common at earlier ages, this disease finds its greatest incidence in advanced years, especially after eighty-five years. The explanation of this fact involves some difficult questions.

Most rodent ulcers are derived from hair follicles, others from congenital epidermal rests. Long-continued chronic irritation doubtless plays a rôle, but it seems necessary to assume that the senile atrophy of the skin does not equally affect all hair follicles and that some chronically irritated follicles retain powers of growth which enable them to proliferate and acquire malignant properties. Thiersch's theory of diminished resistance of connective tissues has been commonly employed in this connection. Indeed one may here point out an important principle which governs senile atrophy in all organs, namely, that during the atrophic process surviving epithelial tissues may not only escape atrophy, but may exhibit increased powers of growth which tends to assume malignant properties. This principle is also exhibited in the sudden and excessive growth of single hairs which often appear on the skins of aged persons. The complete explanation of the phenomenon, as usual, escapes our detection, but the observation must be regarded as one of the most important data on which tumor growth may be referred to the aging process.

Mammary Cancer. After the skin, the female breast, in Bashford's tables, shows the most notably increased incidence after sixty-five years, and especially after seventy-five years. This fact is not generally recognized. I have been unable to determine that mammary cancer in the aged presents any characteristic features. Generally, the cancers of the aged run a slow course, but in the breast there are not a few cases in which the disease is unusually rapid and the structure highly atypical and malignant. A rapidly growing hemorrhagic carcinoma of the nipple, observed at the Memorial Hospital, illustrates this group. It does not appear clearly that scirrhus cancer is more common in the aged than at earlier periods. While the precancerous changes in these cases doubtless occupy many years, the actual outbreak of the disease must be referred to the conditions belonging to the senile period. The rapid course of certain cases must be referred to inherent properties of the tumor cells, and not to lack of defensive mechanism in the atrophic sclerosed tissues, since the latter factors are present in the scirrhus cases.

Gastric Cancer. Cancer of the stomach shows its highest relative incidence between sixty-five and seventy-five years (Bashford), and it remains high after eighty-five years. I know of no data which may explain this fact, nor of any peculiar features of gastric cancer in the very aged. Horsley reports 5 cases of gastric carcinoma without peculiar features in subjects over seventy years of age, and comments on the favorable results of operation upon them. After sixty-five years, I have observed nearly all forms of gastric cancer, except the bulky adenocarcinoma. These include early adenocarcinoma of the pylorus, diffuse fibrocarcinoma of the pylorus, diffuse sclerosing carcinoma, linitis plastica, and probably one very remarkable case of ulcero-carcinoma in a female aged seventy-three years, of thirteen years' duration. However, linitis

plastica occurs at earlier ages, and the slow course of fibrocarcinoma must be referred more to the intrinsic properties of the cells than to any factor residing in senility. Increasing glandular atrophy, muscular atony, arteriosclerosis, imperfect mastication, mouth infections, peritoneal bands, and intestinal stasis, may all play a part in the eventual outbreak of gastric cancer in the aged. None of these factors are peculiar to old age, but the lapse of time may permit them to become effective.

Rectal and Sigmoidal Cancer. Rectal and sigmoidal cancer also shows its highest incidence after sixty-five years, and it seems safe to refer this fact to long-continued rectal irritation from fecal stasis, anal disease, prostatic enlargement, and other pelvic obstructions.

Cancer of the Lip and Tongue. Cancer of the lip and tongue in males increases in frequency rapidly after sixty-five years, and very rapidly after eighty-five years. It is not difficult to find the explanation in the cumulative effects of the well-known forms of chronic irritation which are responsible for these lesions at earlier periods.

That cancer of the entire alimentary tract becomes so very frequent in aged subjects may well be emphasized. Whether the chronic irritations or the acquired predisposition of the tissues are the more important factors may be debatable, but the facts seem to call for special cautions and hygienic efforts directed to the prevention of these forms of cancer. In the aged their prognosis is extremely unfavorable.

Uterine Cancer. While the greatest number of deaths from this disease falls in the fifth decade, and at a comparatively early age, the highest incidence in proportion to the number of women living is not reached until after sixty-five years, and the proportion remains high to the end of life. Corpus carcinoma especially belongs to the later periods. The typical corpus carcinoma of elderly women and spinsters occurs in a small atrophic uterus and usually involves the entire endometrium. It arises on the basis of atrophic endometritis, in which isolated glands escape atrophy and proliferate slowly. These cases illustrate the principle already stated of the malignant proliferation of isolated cell groups in an atrophying organ. Although exactly similar conditions arise in earlier periods, when precocious atrophy occurs, the disease must be assigned essentially to senescence.

Ovarian Tumors. These are frequent in early ages, and are well distributed over other periods, but there is a notable group of very malignant, rapidly fatal cases occurring in old subjects. I have observed two very anaplastic adenocarcinomas in subjects over eighty years. Isbruch and Werdt both report cases of peculiar granulosa-cell tumors of the ovary, and state that they occur in older women, and are associated with endometrial hypertrophy. However, 3 of Werdt's 6 cases occurred in young subjects.

These very late cases of very anaplastic carcinoma of the ovary are highly interesting, since they occur in atrophic organs forty and

fifty years after functional activity has virtually ceased. They reveal the cancer cell in a sinister light. It may be assumed that in the old atrophic ovary, growth restraints are almost wholly lacking, but the enormous powers of growth of these long slumbering cells are one of the marvels of the tumor world.

Cancer of the Liver. Since the majority of tumors of liver and gall bladder are sequels of long-standing cirrhosis, or cholelithiasis, it is not surprising that the greatest incidence of these tumors occurs at a late period—sixty-two years. (Lazarus-Barlow.) Yet, only two forms of liver cancer appear to be characteristic of old age. One of these is the cancerous cirrhosis, in which an old cirrhotic process terminates slowly in a general cancerous degeneration of the incarcerated liver lobules.

Another form, even more characteristic, is the solitary malignant hepatoma, which while generally occurring in middle life, may appear in elderly subjects without any previous cirrhosis, or premonitory symptom, and run a very rapid course. In one case I found, as the sole symptom, a single fatal hemorrhage into the peritoneum.

Cancer of the Gall Bladder and Bile Ducts. Cancer of the gall bladder and bile ducts, producing a very large liver with jaundice, has a late average incidence, and was long ago classed by Frerich with the essential cancers of old age. The average age, in Futterer's large series was fifty-seven years.

Pancreatic Cancer. The two main forms of pancreatic cancer, one arising from the ducts, the other from the parenchyma, generally follow chronic inflammation of the pancreas, so that the age of incidence of this disease is late. Lazarus-Barlow gave the average age at sixty years. Bard and Pic report several cases after seventy years, and point out the cardinal symptoms; distention of the gall bladder, jaundice, absence of hepatic enlargement, and rapid cachexia.

Cancer of the stomach, liver, gall bladder and pancreas, being inaccessible lesions, probably accounts for the death of many old persons in whom no accurate diagnosis is recorded.

Prostatic Cancer. Cancer of the prostate gave the highest average age incidence in the report of Lazarus-Barlow (seventy-two years). The explanation lies in the fact that this disease usually arises on the basis of chronic prostatitis, which is seldom well established before the sixtieth year. It, therefore, deserves recognition as one of the prime cancers of old men.

Renal Tumors. The various renal tumors are well distributed over all ages, from infancy to middle life, but there is one form of renal cancer which belongs exclusively to old age. This is the multiple adenocarcinoma arising in old arteriosclerotic kidneys. It is of little clinical interest because of its rarity. That many of the ordinary renal and adrenal carcinomas may be expected in old age, is shown by Bashford's reports in which the highest proportional

incidence came between seventy-five and eighty-five years, following a marked increase after fifty-five years.

Bladder Tumors. Although many carcinomas of the bladder occur in old persons, this disease shows no definite relation to old age. In the male, Lazarus-Barlow found two groups, one occurring at fifty-two years, and the other at sixty-seven, but neither of the groups was numerous, and no difference in the etiologic factors was mentioned.

Tumors of the Brain. Tumors of the brain are generally regarded as diseases of early and adult life, but Bashford's tables show a steady increase in proportional incidence up to sixty-five years. Age, therefore, enjoys no immunity to the outbreak of these neoplasms. In the report of Bailey and Cushing, it appears that the spongioblastoma (gliosarcoma), was the only tumor occurring with any great frequency in elderly subjects. This tumor was most frequent in the fifth decade, while the oldest subject was sixty-nine years of age. The etiology of these tumors shows little connection with factors of old age.

Sarcoma. The great immunity of old age to sarcoma finds its main explanation in the reduced activity of the connective tissues, and the early maturation of the bony skeleton. Rarely one observes late myosarcomas of the uterus and gastrointestinal tract and a few neurosarcomas. In the field of bone sarcoma, it is worthy of note that the only osteosarcomas reported in the Registry of Bone Sarcoma, in subjects over fifty years of age, developed on the basis of osteitis fibrosa. In the literature there are a few reports of multiple giant-cell tumors in old persons, usually in connection with osteitis fibrosa.

Summary. The attempt to summarize the conclusions to be drawn from the foregoing data requires the admission that the material is very miscellaneous, fragmentary and inconclusive. The statistical studies prove that the chance of dying of cancer increases up to the end of life, and that this chance is increasing, mainly because people are living longer, possibly also because the exposure to cancerigenic agents and habits is greater. These facts alone are of little clinical or pathologic importance, since they do not prove that all or any great number of these cancers result from the processes of senescence. The mere lapse of time accounts for many and may possibly account for the majority of the cancers of the aged.

I have been unable to find any report of a study of a large number of cases of cancer in old subjects, with the object of determining to what extent the disease was the result of senescence. Such an undertaking would be very difficult and laborious, so much so, that no one seems to have been willing to attempt it. The various textbooks on diseases of old age contain very meager reference to the subject. Only Schwalbe attempts a systematic enumeration of the tumors of old age, but without critical analysis. Yet, a few facts of

medical importance seem to stand out prominently. Senile atrophy of tissues and organs, replacement, fibrosis and arteriosclerosis create local conditions which favor the development of some cancers which may be properly attributed to old age. Some of these true cancers of the aged exhibit peculiar clinical and pathologic features, and several tumors of this type have been enumerated in the previous discussion in this paper. They are, on the whole, not numerous.

During the senile atrophy of tissues and organs, it seems to be a principle of importance that isolated cell groups, gland acini, lobules, and probably tissue rests, escape atrophy and find conditions of growth more favorable. The data support Thiersch's theory of disturbed balance between epithelium and connective tissue.

In this crude sense, cancer may be considered a function of senescence. But, if all other causes of death were eliminated, pneumonia would become the main cause of death of old persons, and in the same sense become a function of senescence.

The main factor which accounts for the high incidence of cancer in the aged is the lapse of time, which permits the natural termination in cancer, of processes which have their inception in adult life, or in youth, in infancy, or even *in utero*. This principle applies to nearly all the tumors arising from tissue abnormalities, and to a great many of those resulting from chronic irritation. That the great majority of tumors of old age may be thus explained, cannot be asserted without much more evidence than is now available, but appears highly probable.

Arteriosclerosis probably plays an important rôle in the development of many cancers in the aged, but it is by no means a constant factor, and its exact significance has never been determined.

If precocious atrophy and arteriosclerosis of single organs are regarded as a phase of senescence, then a strict chronologic classification of cases is unsound, and many cancers occurring in adult and middle life belong in the group of cancers of old age.

Probably the majority of cancers occurring at advanced age periods show exactly the same etiologic factors and clinical course as those occurring in adult and middle life, and their separation as a specific group is unwarranted.

For the same reasons, cancer in the aged must be regarded as always pathologic and not as an essential phase of the process of senescence. Senility merely acts in preparing the soil and rendering the tissue more susceptible to the action of the usual exciting factors, the presence of which is almost as essential as in earlier periods of life.

In general, the cancers of old age pursue a relatively slow course, depending on the reduced metabolism of this age period, but there are many cases which exhibit an unusually rapid growth. These latter probably arise mainly from tissue rests, which have long remained quiescent, but which, when once excited to growth, find conditions especially favorable for unrestrained proliferation.

In the clinical course of cancers in the aged, secondary infection plays a very prominent part and often masks the true nature of the disease. Hence the proportion of unrecognized cancers is higher in the aged than at other periods. Owing to the very high incidence of cancer in the aged, the suspicion of this disease should be kept prominently in mind by diagnosticians.

For the same reasons, special precautions against the outbreak of cancer may well be employed in the very aged.

The detailed study of the action of factors essential to senescence in the origin of cancer in the aged is at present quite inadequate to determine the real influence of old age on the incidence of cancer. Until such studies are available, most of our conclusions in this field must be subject to many limitations.

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A SERUM TEST FOR THE DIAGNOSIS OF CANCER BASED ON A NEW THEORY OF ETIOLOGY.

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NUMEROUS serologic tests for the diagnosis of cancer have been proposed. Although some of these have gained a certain popularity, most of the tests which have been described have failed to survive critical repetition and no serodiagnostic test is today generally regarded as reliable and specific. It is the purpose of this paper to propose a test for the diagnosis of malignant disease based upon principles which differ fundamentally from any of the known tests which have been proposed and to describe the results obtained which are believed to substantiate the proposed theory. Diagnostic tests

for cancer based upon the principles of immunity factors were first attempted by means of complement fixation. These were soon followed by others based upon chemical precipitation and still later by flocculation tests.

In a thorough historic review of the subject, Fry¹ points out that the complement-fixation test which has been extensively used to discover antibodies in the serum was first advocated by Sampietro and Tesa² in 1908. Subsequent observers, however, failed to substantiate the results claimed for this test. Other reactions such as the precipitin test used by Engel in 1904, the anaphylactic test studied by Pfeiffer and Finstern³ and the antitryptic reaction described by Marcus⁴ have given variable results. The fallacies of the ferment reaction of Abderhalden were pointed out by Leitch⁵ in 1914. A chemical precipitation reaction was described by Kahn and a similar one by Botelho.⁷ The latter has been shown by Fry⁸ to be of little diagnostic value. The flocculation method was first used by Weil and Braun⁹ and followed by a test based on the same principle by Roffo.¹⁰

Lavedan,¹¹ using Botelho's reaction on an extensive series of well-controlled cases, concludes that the test is not specific for cancer, that it is not a reaction of cachexia, being often positive in patients with localized lesions and negative in cases of advanced cancer. The exactness of the results depend upon the location of the lesion. In deep-seated cancer (breast, uterus, digestive tract) the percentage of exact results is high and the test has a real diagnostic value. An analysis of the Botelho serum reaction by Baty and Greene¹² of the Huntington Memorial Hospital, also led to the conclusion that the reaction is of no value in the diagnosis of cancer. A flocculation test described by Brossa, Bozzolo and Lombardi¹³ gave clearly positive results in growths of the gastrointestinal tract. Noncancerous patients gave positive results in advanced cases of tuberculosis and lues, otherwise, controls were negative. Occasional negative results occurred in lesions of the skin.

In a series of 500 cases of malignant and non-malignant disease, Fry reports 75 per cent correct results. Out of 239 cases of malignant disease, 170 gave positive results (71 per cent) and out of 261 controls, 204 gave negative results (78 per cent). Healthy individuals gave uniformly negative results. Non-malignant tumors usually gave a negative reaction. Positive flocculation occasionally occurred in acute febrile conditions such as tuberculosis and sepsis. The antigen employed was obtained from carcinoma of the breast. A special study of the Thomas-Binetti reaction by Mondain, Douris and Beck^{14, 15} led to the conclusion that the results have been obtained because of the fact that the neoplastic extract was not aseptic and they attributed the discoloration of the methylene blue to microbic action. They conclude that cancer serum has not the power to reduce methylene blue.

Theoretical Considerations. As a working hypothesis, it may be assumed that in the ordinary course of normal cell growth, each type of cell produces a lysin against the other type of cell. That is to say, connective-tissue cells normally have the property of generating certain lysins which are antagonistic to excessive growth of epithelial cells, so that although an inciting factor such as chronic irritation may be present, carcinoma does not develop. If, on the other hand, the connective tissue fails to produce such lytic agent, a carcinoma results when the proper extrinsic factors are present. The opposite cycle follows in the production of sarcoma, that is, a deficiency or lack of lytic agent normally produced by epithelial tissue results in the presence of proper extrinsic factors in the production of sarcoma. In other words, the maintenance of an equilibrium between the connective and epithelial tissues is considered as dependent upon the presence of antagonistic lytic agents. The hypothesis of Waldeyer and Thiersch of an equilibrium between the connective tissue and epithelial elements and the tissue tension hypothesis of Ribbert, are in direct accord with this theory. The ability of normal serum and the failure of cancer serum to autolyze cancer cells *in vitro* has been demonstrated (Freund and Kaminer¹⁶) and points to the presence of a lytic substance in normal blood serum.

This theory is also in accord with the general nature of opposing physiologic forces found in normal biologic activities, where two counteracting principles tend to maintain an equilibrium in normal cell growth, that is, the maintenance of the endocrine balance, the vascular functions of dilatation and constriction and the thermogenetic and thermotactic apparatus.

Based on this conception of the possible cause of malignant disease, it was believed that a lytic agent might be produced by the inoculation of animals with purely embryonic epithelial cells in the case of carcinoma, and connective-tissue cells in the case of sarcoma. In this way, amboceptors would be developed in such treated animals and their sera might have the property when injected into a patient suffering from malignant disease to destroy, in case of carcinoma, embryonic epithelial cells, and in the case of sarcoma connective-tissue cells, based upon the accepted serologic principles of the production of lytic agents.

The second consideration was to demonstrate the correctness of the relationship between malignant new growth and the lytic agent produced by immunizing animals. Experiments were performed to prove the existence of such amboceptors on the basis of the production of precipitins, recognizing that if precipitins were formed between the amboceptor and the serum of a cancer patient, a homologous relationship would be established and it would be demonstrated that no difference exists between embryonic cells of one species of animal and another. In order to determine whether the

precipitin reaction is due purely to the immunizing properties of the embryonic cells, control animals were inoculated with pancreatic tissue obtained from mature animals and it was found that the sera of these animals failed to produce precipitin when brought in contact with the serum of cancer patients. According to J. Ewing, this may be due to the presence in embryonic tissue of specific growth-stimulating substances. Having demonstrated the specificity of the amboceptor produced by immunizing animals with embryonic cells, it was logical to attempt to utilize this immunologic principle as a diagnostic test.

It is important to point out that the principle upon which, the present test is based, differs fundamentally from that of any other test which has been presented in the following ways: (1) Because the test is purely biological in character, and (2) because the amboceptor is produced by means of purely embryonic cells. It should be noted that most of the serodiagnostic tests in which tissue cells have been used have been performed with an antigen composed of both epithelial and connective-tissue cells. Fry, for instance, used breast cancer as an antigen, but adds that cellular carcinoma is preferable to scirrhus cancer. When the theory upon which this test is based is considered, it is readily seen that the presence of adult connective tissue detracts from the specificity of the antigen and it is suggested that this factor may be responsible for the better results obtained with the more cellular growths. It is believed that the complement-fixation test for cancer could be rendered specific if pure embryonic cells such as are employed in our test were used in the preparation of the antigen. Attempts to utilize this principle in a complement-fixation test are under way.

Methods. Preparation of Amboceptor Preliminary Steps. It is essential that in the preparation of the amboceptor both for carcinoma and sarcoma, all glassware and other utensils used be chemically clean, sterile and of a neutral reaction. The serum of the animals is obtained according to the usual method in test tubes of large caliber and allowed to coagulate at room temperature. It is then placed in the incubator for a few hours and then placed in the ice chest to obtain separation of the serum without hemolysis. The serum is then pipetted off into sterile centrifuge tubes, and is then centrifuged to throw down any blood cells which may have remained, so that the serum may be rendered free of substances like chyle, blood cells, and so forth.

Preparation of the Amboceptor for Carcinoma. Mammalian embryos are used (calves, sheep, pigs). They must not be in a later stage than the second month of pregnancy. This is readily recognized by their relative smallness, and by the smoothness of the skin (for instance, there is no formation of hair). In securing these embryos, the abdomen must be opened under sterile conditions. The pancreas and submaxillary glands are dissected out,

and placed in a sterile dish. A hypotonic salt solution is poured over these, and if possible, allowed to freeze, the object being to permit an easier removal of the fibrous capsule. The capsule and the ducts, and so forth, are then removed by careful manipulation with small tissue forceps. The epithelial tissue is picked out. It is placed in a mortar in which sterile copper gauze is inserted (to facilitate the maceration) and macerated. Salt solution is added and thoroughly mixed and rubbed up with the macerated tissue until the fluid becomes milky or opalescent in appearance.

The next step is to inoculate healthy male rabbits intraperitoneally or intravenously as follows: (The method used by the author was the intraperitoneal one.) The inoculations are made three days apart. The first injection was 3 cc.; second injection, 5 cc.; third injection, 7 cc.; fourth injection, 10 cc. and fifth injection, 15 cc. The animal is sacrificed three days after the last injection and serum obtained. The amboceptor is now tested with known positive carcinomatous serum and with a known negative serum, as per procedure given below. Precipitin formation should take place with the positive serum; and no reaction with the negative serum.

Preparation of the Amboceptor for Sarcoma. Umbilical cords are obtained freshly. The blood is squeezed out; the veins are punctured and the blood washed away. It is then cut up in small pieces and placed in a meat press. The Wharton jelly (which must be clear of blood) is placed in a mortar, together with bone marrow obtained from embryos (calves, pigs, sheep, etc.), This is well macerated and mixed. It is then filtered through gauze to clear away the small particles of bony substance which might be present. To this, one-third its volume of salt solution is added and is well shaken. Rabbits are inoculated with the mixture every three days, starting with 1 cc. and increasing the dose 2 cc. at every inoculation until five inoculations have been given. The animal is then sacrificed two days after the last inoculation. The serum is obtained as per the previous method for carcinoma. Then it is tested with a known positive sarcomatous serum and with a known negative serum as per procedure given below. Precipitation should take place in the positive serum and no precipitation in the negative serum.

Preparation of the Patient's Serum. As in the preparation of the amboceptor, it is essential that all glassware and other utensils used for the test be chemically clean, sterile and neutral. The serum of the patient is then obtained in the usual manner, and this is done in the morning before the patient has had any food. In order to insure a clear serum, it is preferable to use an 18-gauge needle and a wide test tube. The blood is allowed to coagulate at room temperature. The serum is placed in an incubator for about two hours to secure separation without hemolysis.

Technique of Test. Three small test tubes are placed in a rack. In the first tube 0.3 cc., of amboceptor is placed and carefully over-

layered with 0.9 cc. of patient's serum to which complement had been previously added (3 minims per cc.), (if the serum is older than twenty-four hours). This is overlaid with 0.2 cc. of half normal saline. In the second tube is placed 1 cc. of patient's serum, + 0.4 cc. of half normal saline. In the third tube is placed 1 cc. of amboceptor + 0.4 cc. half normal saline. The rack is then placed in the incubator for five hours without being disturbed. It is advisable to perform two similar tests using a known positive and known negative control as in the Wassermann reaction. After five hours the test is read. Each tube is carefully removed from the rack so as not to disturb the point of contact between the different fluids and is placed against a dark background so as to permit an indirect illumination. In a positive reaction, the result is indicated by a fine white ring at the point of contact of the fluids and a turbidity extending downward. A negative reaction is indicated by the absence of a ring or turbidity, the entire fluid remaining clear. Readings should be recorded as strongly or faintly positive depending upon the degrees of turbidity obtained.

Simplified Modification of Test. In an attempt to simplify the test and make it more useful for practical purposes, it seemed plausible to attempt to utilize the embryonic tissues directly in the form of an antigen instead of the amboceptor produced by animal immunization. In this way, the difficulties encountered in the production of the amboceptor would be eliminated. It was found for instance, that very few rabbits were capable of producing a satisfactory amboceptor. A further difficulty was encountered in the turbidity of the serum in some animals. The following technique was employed in the preparation of the antigen.

Antigen for Carcinoma. The embryonic epithelial cells are prepared as described in the above method up to the point of animal inoculation. At this point, the cells suspended in salt solution are centrifuged until the supernatant salt solution is perfectly clear, the salt solution is then discarded and the epithelial cells are placed in a porcelain dish and dried at a temperature of 75° C. to a doughy consistency. During this period, it is essential that the tissue be stirred thoroughly at fifteen-minute intervals in order to permit uniform drying. The tissue is then placed in a glass-stoppered bottle to which is added three times its volume of acetone. The mixture is permitted to stand in the ice chest for twenty-four hours with frequent shaking. The acetone is then poured off and replaced by one and a half volume of fresh acetone for another twenty-four hours. The acetone is again decanted and the tissue is placed in a mortar to which five times its volume of absolute alcohol is added. This is macerated for about fifteen minutes until the alcohol becomes somewhat milky. The mixture is then kept in the ice box for five days during which time it is forcibly shaken at two-hour intervals. The alcohol extract is then decanted and is ready for use.

Antigen for Sarcoma. A mixture of Wharton's jelly and red bone marrow of calf embryo is macerated in a mortar, to which two volumes of salt solution are added. This is placed in a porcelain dish at a temperature of 75° C. until the mixture becomes grayish in color. The salt solution is then decanted and the tissue is placed in three times its volume of acetone for twenty-four hours. The acetone is then decanted and replaced by one and a half volumes of acetone for twenty-four hours. The acetone is again decanted and the tissue is placed in a mortar and macerated with five times its volume of alcohol for fifteen minutes until the alcohol extract assumes a light-brown color. The mixture is then placed in a glass-stoppered bottle in the ice chest for five days, during which time it is shaken at two-hour intervals. The alcohol extract is then ready for use.

Technique of Test. Five to 10 minims (depending upon titration) of antigen is placed in a test tube, to which 30 minims of suspected serum (which has been previously diluted 50 per cent with normal salt solution) is added slowly drop by drop. This is allowed to stand for two minutes. It is then agitated until flocculation takes place. Ten minims of salt solution is added and is allowed to stand for two minutes. It is agitated again and read against a frosted electric light. A positive reaction is indicated by flocculation. A negative reaction produces no flocculation. It is important that the drops be added slowly and at regular intervals. Adding the drops too rapidly might give a negative reaction in positive cases. It is also important to distinguish between air bubbles and true floccula. The former always rise to the surface, whereas the latter settle to the bottom.

If the suspected serum has a very low specific gravity and looks watery it is best not to mix serum with salt solution, but use it in its original state, as adding salt solution is liable to render a positive serum negative.

Titration. A known positive and negative serum are employed in order to determine the least amount of antigen necessary to produce a positive reaction. When this endpoint is reached, the same amount is used on the known negative and should give a negative reaction. It is essential to determine this endpoint accurately and utilize the least amount of antigen necessary to produce a flocculation. If the known positive of this amount is exceeded by even a few minims, a flocculation might take place in the negative serum.

Precautions. The following precautions should be observed in the preparation of the material: It is essential that the capillary pipettes used in the test should be of equal caliber. It is evident that any difference in the caliber of the pipettes would render the test inaccurate. It is also very important that the cells for the antigen and amboceptor be prepared of pure embryonic cells of

the type desired—for example, the capsules and ducts of the pancreas and submaxillary gland must be removed thoroughly so that no remnants of fibrous tissue will be left. In the preparation of the connective-tissue amboceptor as well as the antigen, Wharton's jelly must be free from blood. The antigen must be dried until it assumes a doughy character—not more nor less than that. Special care should be taken to avoid scorching the tissue while drying. It is essential that the drying process be continuous, proceeding to the finish without stopping.

Advantages. The advantages of the modified method over the immunization method are as follows:

1. Elimination of use of animals in the production of amboceptor.
2. Simplicity of test with advantage of flocculation over precipitation method in facility of reading and interpretation.

TABLE I.—RESULTS OF TEST IN KNOWN MALIGNANT TUMORS.

No.	Case.	Location	Pathologic Report.	Serologic Test.
1	T. C.	Rectum	Adenocarcinoma	Positive
2	T. F.	Breast	Schirrous carcinoma	"
3	N.	Cervix	Squamous carcinoma	"
4	P. G.	Breast	Alveolar carcinoma	"
5	C. E.	Rectum	Adenocarcinoma	"
6	E. S.	Antrum	Squamous carcinoma	"
7	E. F.	Face	Basal-cell carcinoma	"
8	K. T.	Esophagus	Squamous carcinoma	"
9	G. V.	Breast	Adenocarcinoma	"
10	T. P.	Lip	Squamous carcinoma	"
11	V. N.	Stomach	Adenocarcinoma	"
12	V. S.	Gall bladder	Adenocarcinoma	"
13	M. H.	Uterus	Adenocarcinoma	"
14	O. N.	Eyelid	Basal-cell carcinoma ?	Negative
15	McP.	Stomach	Adenocarcinoma	Positive
16	A. H.	Mandible,	Squamous carcinoma	"
17	A. R.	Intestine	Adenocarcinoma	"
18	C. P.	Nose	Basal-cell carcinoma	"
19	P. S.	Wrist	Squamous-cell carcinoma	"
20	G. W.	Stomach	Adenocarcinoma	"
21	B. C.	Ulna	Osteogenic sarcoma	"
22	B. T.	Thyroid	Spindle-cell sarcoma	"
23	E. K.	Neck	Spindle-cell sarcoma	"
24	C. B.	Esophagus	Squamous carcinoma	"
25	A. F.	Floor mouth	Squamous carcinoma	"
26	B. 3	Tongue	Squamous carcinoma	"
27	H. O. B.	Lip	Squamous carcinoma	"
28	S. M.	Colon	Adenocarcinoma	"
29	A. R.	Cheek	Squamous carcinoma	"
30	J. F.	Femur	Osteogenic sarcoma	"
31	F.	Tongue	Squamous carcinoma	"
32	S. F.	Breast	Alveolar carcinoma	"
33	M. K.	Breast	Adenocarcinoma	?
34	K.	Breast	Duct carcinoma	Positive
35	W.	Breast	Adenocarcinoma	"
36	B. W.	Cervix	Squamous carcinoma	"
37	W.	Cervix	Squamous carcinoma	"
38	S.	Prostate	Adenocarcinoma	"
39	Dr. K.	Cervix	Squamous carcinoma	"
40	M. G.	Rectum	Carcinoma	"

TABLE I.—RESULTS OF TEST IN KNOWN MALIGNANT TUMORS.

Continued.

No.	Case.	Location.	Pathologic report.	Serologic test.
41	R. L.	Rectum	Carcinoma	Positive
42	I. K.	Stomach	Carcinoma (clinical diagnosis)	"
43	M. E.	Cervix	Squamous carcinoma	"
44	S. Mc.	Breast	Adenocarcinoma	"
45	F. M.	Rectum	Adenocarcinoma	"
46	S. S.	Penis	Epithelioma	"
47	M. H.	Esophagus	Squamous carcinoma	"
48	N. N.	Esophagus	Squamous carcinoma	"
49	M. N.	Rectum	Carcinoma	"
50	Dr. B.	Breast	Adenocarcinoma	"
51	M. J.	Penis	Epithelioma	"
52	M. S.	Face	Basal-cell carcinoma	"
53	N. K.	Stomach	Adenocarcinoma	"
54	M. G.	Stomach	Carcinoma	"
55	M. R.	Stomach	Carcinoma	"
56	S.	Prostate	Carcinoma	"
57	A. H.	Esophagus	Squamous carcinoma	"
58	McD.	Stomach	Carcinoma	"
59	M. O.	Stomach	Carcinoma	"
60	Bed 78	Stomach	Carcinoma	"
61	D. J.	Stomach	Carcinoma	"
62	H. J.	Esophagus	Carcinoma	"
63	R. N.	Stomach	Carcinoma	"
64	J. S.	Stomach	Carcinoma	"
65	P. G.	Esophagus	Squamous carcinoma	"
66	N. B.	Stomach	Carcinoma	"
67	G.	Esophagus	Carcinoma	"
68	N. E. L.	Breast	Adenocarcinoma	"
69	B. W.	Uterus	Adenocarcinoma	"
70	W. E.	Stomach	Carcinoma	"
71	M. H.	Lung	Carcinoma	"
72	A. J.	Breast	Adenocarcinoma	"
73	M. H.	Stomach	Carcinoma	"
74	D. M.	Breast	Adenocarcinoma	"
75	G.	Cervix	Squamous carcinoma	"
76	N. W.	Rectum	Carcinoma	"
77	I. S.	Thyroid	Carcinoma	"
78	J. S.	Pancreas	Metastatic carcinoma	"
79	M. B.	Breast	Alveolar carcinoma	"
80	N. S.	Rectum	Carcinoma	"
81	H. M.	Stomach	Carcinoma	"
82	M.	Rectum	Carcinoma	"
83	M. W.	Stomach	Doubtful histologically	"
84	A. K.	Bladder	Carcinoma	"
85	E. J.	Prostate	Carcinoma	"
86	T. G.	Prostate	Carcinoma	"
87	W. B.	Bladder	Carcinoma	"
88	M. R.	Prostate	Carcinoma	"
89	H.	Breast	Scirrhus carcinoma	"
90	R. S.	Liver	Metastatic carcinoma	"
91	N. M.	Rectum	Carcinoma	"
92	S. R.	Uterus	Carcinoma	"
93	H. C.	Stomach	Carcinoma	"
94	S.	Stomach	Carcinoma	"
95	B. B.	Breast	Alveolar carcinoma	"
96	S. B.	Rectum	Carcinoma	"
97	R.	Rectum	Carcinoma	"
98	R. R.	Esophagus	Carcinoma	"
99	W.	Bladder	Papillary carcinoma	"

TABLE I.—RESULTS OF TEST IN KNOWN MALIGNANT TUMORS.

Continued.

No.	Case.	Location.	Pathologic report.	Serologic test.
100	R. W. 4	Breast	Adenocarcinoma	Positive
101	L. P.	Liver	Metastatic carcinoma	"
102	K. 3	Tongue	Carcinoma	"
103	L. 4	Antrum	Carcinoma	"
104	D. 5	Cervix	Carcinoma	"
105	S. S.	Larynx	Squamous carcinoma	"
106	F. J.	Cervix	Carcinoma	"
107	J. S.	Cervix	Carcinoma	"
108	7 W.	Bladder	Carcinoma	"
109	9 M.	Mouth	Carcinoma	"
110	R. W. 4	Rectum	Carcinoma	"
111	H.	Rectum	Adenocarcinoma	"
112	S.	Penis	Epithelioma	"
113	S. H.	Larynx	Carcinoma	Doubtful
114	M. W.	Cervix	Carcinoma	Faintly
115	S. Z.	Cervix	Epithelioma	Faintly positive
116	M. A.	Breast	Carcinoma	Positive
117	M.	Cervix	Carcinoma	Negative
118	H. H.	Rectum	Carcinoma	Positive
119	E.	Breast	Carcinoma	"
120	H.	Tongue	Carcinoma	"
121	P. 17	Rectum	Carcinoma	"
122	G.	Uterus	Adenocarcinoma	"
123	W.	Uterus	Carcinoma	"
124	T.	Uterus	Carcinoma	"
125	W. S.	Lip	Carcinoma (clinically)	Negative
126	C.	Cervix	Carcinoma	Positive
127	D. E.	Rectum	Carcinoma	Faintly positive
128	G.	Cervix	Squamous carcinoma	Positive
129	G.	Rectum	Adenocarcinoma	"
130	R.	Breast	Alveolar carcinoma	"
131	M.	Stomach	Adenocarcinoma	"
132	C.	Stomach	Carcinoma	"
133	M.	Bladder	Infiltrating carcinoma	"
134	G. L.	Gall bladder	Carcinoma	"
135	R.	Stomach	Adenocarcinoma	"
136	S.	Ilium	Osteogenic sarcoma	"
137	F.	Stomach	Adenocarcinoma	"
138	O.	Colon	Gelatinous carcinoma	"

TABLE II.—RESULTS OF TEST IN KNOWN BENIGN TUMORS.

No.	Case.	Location.	Pathologic report.	Serologic test.
139	H. A.	Leg	Neurofibroma	Negative
140	E.	Breast	Papillary cystadenoma	Positive
141	W. F.	Uterus	Myoma	Faintly positive
142	B. F.	Uterus	Myoma	Negative
143	S. G.	Uterus	Myoma	Positive
144	T. B.	Breast	Benign cyst	Negative
145	S. C.	Uterus	Myoma	"
146	C. L.	Uterus	Myoma	"
147	C. C.	Breast	Benign cyst	"
148	M. I.	Uterus	Myoma	"
149	M. C.	Uterus	Myoma	"
150	O.	Bladder	Papilloma	"
151	S.	Back	Lipoma	"

TABLE II.—RESULTS OF TEST IN KNOWN BENIGN TUMORS.
Continued.

No.	Case.	Location.	Pathologic report.	Serologic test.
152	P.	Uterus	Polyp	Negative
153	R.	Uterus	Myoma	"
154	M.	Uterus	Myoma	"
155	J.	Uterus	Myoma	"
156	P.	Uterus	Myoma	"
157	T.	Ovary	Simple cyst	"
158	R.	Uterus	Myoma	"
159	E. D.	Jaw	Epulis	"

TABLE III.—RESULTS OF TEST IN NON-MALIGNANT DISEASE.

Disease.	No. of cases.	Negative.	Positive.
Endometritis	12	12	0
Diabetes	72	70	2
Lues	61	60	1 (Leukoplakia of tongue)
Pernicious anemia	3	3	0
Nephritis	27	27	0
Thyroid disease	156	152	4
Tuberculosis	5	5	0
Osteomyelitis	4	3	1 (Faintly pos.)
Mastitis	5	5	0
Amebic dysentery	1	0	1*
Polycythemia	2	2	0

* Serum contained chyle.

TABLE IV.—RESULTS OF TEST IN NORMAL ADULTS.

No. of cases	146
Negative	143
Positive (faintly positive)	3

Summary and Conclusion. 1. The theory has been proposed that normal tissue equilibrium is dependent upon a balance maintained by the opposing action of lytic agents produced respectively by connective tissue and epithelial cells and that neoplasia is the result of a lack of such lytic agents on the part of the tissue invaded.

2. Based upon this theory a diagnostic test for malignant disease has been developed.

3. The principle of this test is based upon the homologous relationship between embryonic cells and the sera of patients suffering from malignant disease.

4. The homologous nature of embryonic cells of different mammals has been demonstrated by the ability to develop amboceptors and antigens with embryonic cells of different mammals.

5. A new source and technique for obtaining embryonic cells has been developed and described.

6. This test has been employed in a group of cases of malignant and non-malignant disease and results obtained which tend to substantiate the proposed theory and validity of the test.

7. The results obtained are of theoretical interest in substantiating the proposed hypothesis and are believed to be of practical importance in the serodiagnosis of carcinoma and sarcoma.

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THE DIFFERENTIAL DIAGNOSIS OF PRIMARY AND SECONDARY CARCINOMA OF THE BRONCHI.

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In a recent paper on primary carcinoma of the bronchi by McCrae, Funk and Jackson¹ attention was called to the growing importance of this lesion as a clinical entity. In a study of cases collected from the literature and 14 cases personally observed they conclude that carcinoma of the lung originates in the majority of instances from the bronchus and that this form of carcinoma is increasing in frequency. They emphasize the necessity for bronchoscopy in early diagnosis so that proper treatment may be instituted and call attention to the fact that the early symptoms are those of bronchial irritation and the early signs those of bronchial obstruction. In a study of several recent cases I have been particularly impressed by two points of special diagnostic importance brought out in their work. The one is the frequency of secondary abscess formation in the lung peripheral to the new growth (due to the bronchial obstruction). Under such circumstances, the symptoms and signs of pulmonary abscess may so dominate the clinical picture as to

obscure the diagnosis of the underlying lesion, that is, the bronchial carcinoma.

The second point is that metastases from bronchial carcinoma to the nervous system, abdomen or bones may produce striking clinical manifestations and thus obscure the evidence pointing to the original new growth. This was particularly emphasized in an earlier paper by Fried² who was more impressed than the above-mentioned authors with the tendency of bronchial carcinoma to extrathoracic metastases. An unusual example of such an occurrence was reported by Thomas, Hirsch and Blaine.³ They recorded a case in which the clinical symptoms throughout were associated with alterations of the bones due to metastasis from a primary carcinoma of the bronchus which was not found until an examination of the lungs had been completed some time after the postmortem examination.

One additional feature that enters into the question of the diagnosis of bronchial carcinoma and serves as a special basis for this report is the exact reverse of the point just mentioned; in other words, the occurrence of metastases from an extrathoracic new growth to tracheobronchial lymph nodes causing bronchial compression (and in certain instances actually invading bronchial wall) thus producing chest symptoms and signs simulating primary bronchial carcinoma.

The first case to call my attention to this possibility follows:

Case Reports. CASE I.—A. K., aged fifty-one years, a white man, was admitted to the service of Dr. Chevalier Jackson, October 14, 1927. He complained of cough with slight expectoration of mucus, shortness of breath, huskiness of the voice and loss of weight. The family history was negative. The past history was essentially negative.

The present illness began about a year ago with cough and expectoration which gradually increased in amount. For about three months before his admission there was considerable loss of weight, and shortness of breath became troublesome. During the same period, because the Wassermann test was reported positive, 20 intravenous injections had been given.

Physical examination on admission showed a fairly well-nourished patient with slight dyspnea. The fingers were clubbed. The larynx showed congestion of the mucous membrane, and the left side appeared fixed; the left ventricular band was inflamed and enlarged, and overhung the left cord. The neck was negative. The heart was apparently normal in size and no abnormal sounds were heard. Expansion was limited and the percussion note was dull over the lower two-thirds of the right chest. The breath sounds were tubular and distant and many large musical râles were heard. The left lung was clear and resonant throughout and the breath sounds were exaggerated. Physical examination otherwise was negative. The temperature on admission varied between normal and 101°, the pulse rate was 100 and the respirations 30. The expectoration varied from 6 to 14 ounces in the twenty-four hours. On standing it separated into two layers of which the lower was practically clear and consisted of about 75 per cent of the total quantity. Repeated examinations failed to show tubercle bacilli. The blood Wassermann test was negative and urine examinations were practically negative.



FIG. 1.—Case I. Abscess of lung, with fluid level, lower portion of right upper lobe, secondary to bronchial compression caused by metastatic new growth.

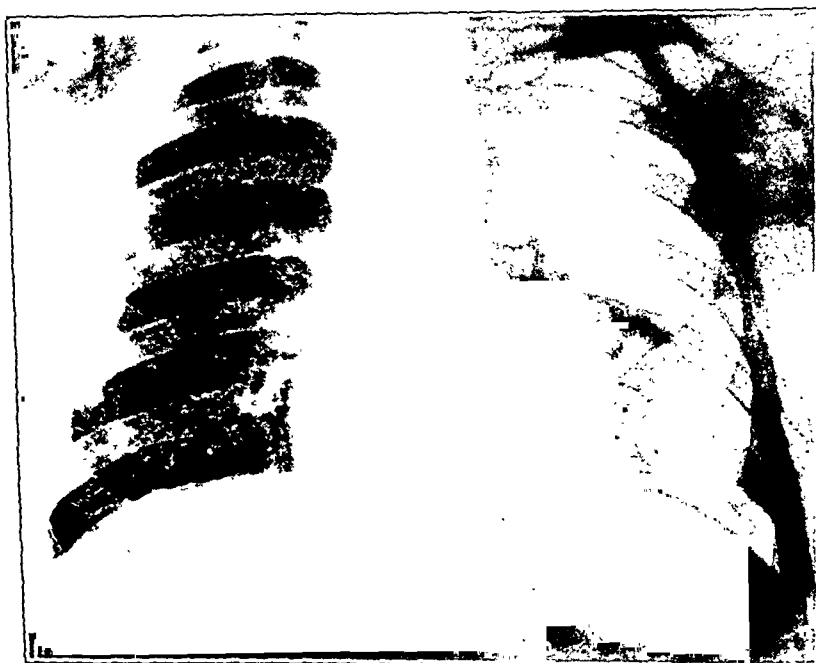


FIG. 2.—Case II. Obstructive emphysema of left lung due to bronchial compression from enlarged lymph nodes. Note the nodular enlargement at the root areas due to metastases from a pancreatic carcinoma to tracheobronchial lymph nodes.

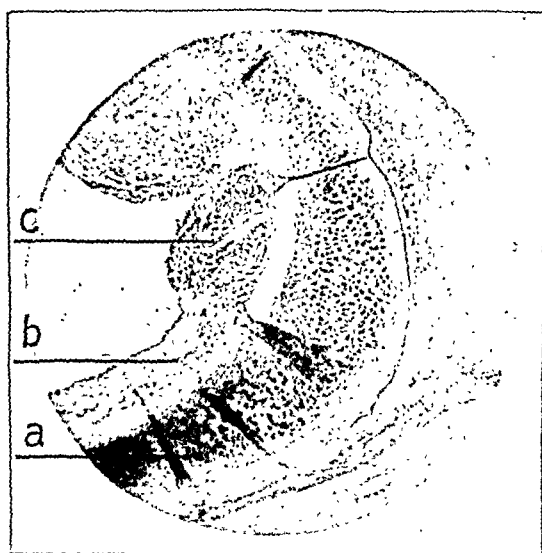


FIG. 3.—Case II. Direct invasion of bronchial wall by metastatic new growth (carcinoma of the pancreas): (a) bronchial cartilage; (b) normal bronchial mucosa; (c) replacement of mucosa by invading carcinoma.

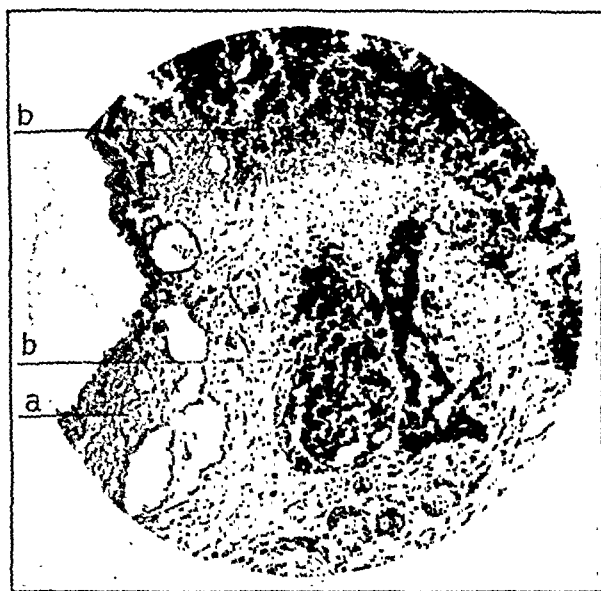


FIG. 4.—Case II. Higher magnification of bronchial mucosa seen in Fig. 3, showing the nature of the carcinomatous invasion: (a) bronchial mucosa; (b) carcinomatous areas.



FIG. 5.—Case III. Area of increased density (abscess and consolidated tissue) middle portion of right lung, peripheral to a primary carcinoma of the right main bronchus.

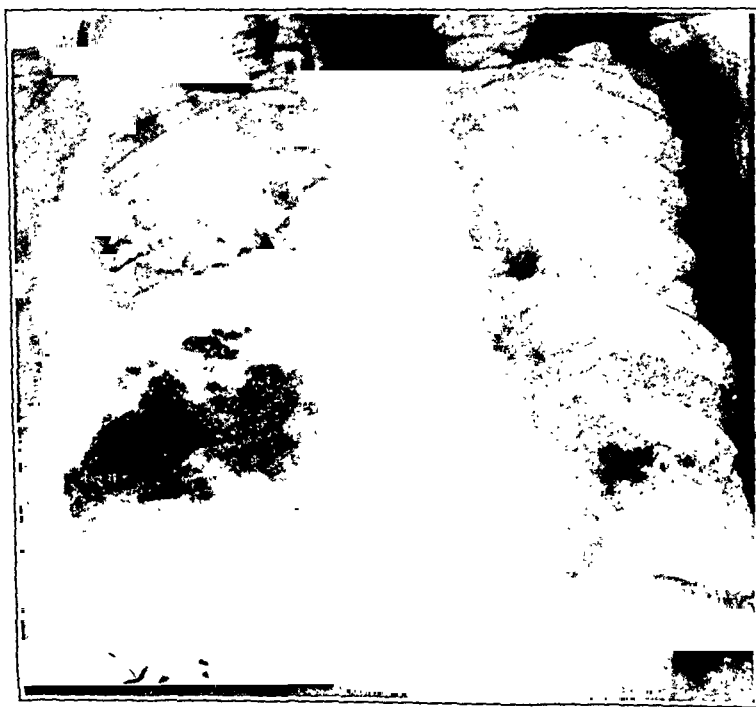


FIG. 6.—Case IV. Showing the usual form of pulmonary metastasis from extra-thoracic new growth.

The Roentgen ray examination of the chest (Fig. 1) showed a rather large cavity in the right apex and another cavity in the lower portion of the right upper lobe with a definite fluid level. This was in fairly close relation to the root of the lung. These areas were thought to be lung abscesses. Bronchoscopy for diagnosis was done by Dr. L. H. Clerf on October 26. "The mucosa of the trachea, carina and right main bronchus was congested. The carina was somewhat broader than normal; the orifice of the right main bronchus was slightly compressed by the crowding inward of the right wall. At about the level of the middle-lobe bronchus, there were found small masses of tissue suggesting granulations which bled very readily when touched. Several small masses were removed for microscopic study. The lumen of the bronchus at this point was definitely constricted; it seemed rigid and fixed. No attempt was made to explore the bronchus beyond this point." The bronchoscopic diagnosis was stenosis of the right bronchus probably due to neoplasm of the right bronchus. Histologic examination of the tissue removed showed evidence of carcinoma and the conclusion, therefore, was carcinoma of the bronchus.

The patient lost ground very rapidly and died on November 6, 1927.

Necropsy (Dr. B. L. Crawford) showed that the right main bronchus was compressed by enlarged lymph nodes. There was a mass of these nodes in the mediastinum, on the right side of the trachea and along the right main bronchus. The nodes were firm and gray, and many measured several centimeters in diameter. The right upper lobe bronchus opened into a large cavity which communicated with several smaller ones, all occupying the upper lobe of the lung. Indurated lung tissue surrounded the cavities.

Examination of the abdomen showed a mass occupying the head of the pancreas. It was firm, grayish tissue which merged with pancreatic substance but could be easily differentiated. Similar nodules were found in the liver, the kidney and adrenals and on the surface of the large gut.

The anatomic diagnoses were: primary carcinoma of the head of the pancreas with metastasis to mesenteric, retroperitoneal, mediastinal and peribronchial lymph nodes and also to the liver, kidney, adrenals and colon. Abscess of the upper lobe of the right lung secondary to bronchial obstruction caused by enlarged lymph nodes.

Comment. This case illustrates how an abdominal tumor with metastases to mediastinal lymph nodes may cause bronchial compression producing symptoms and signs of chest disease which dominate the clinical picture. In the present instance, bronchoscopy with biopsy did not establish the secondary nature of the bronchial new growth. Moreover, even at postmortem up to the time that the primary new growth was found in the head of the pancreas it was thought that the cancer was primary in the bronchus.

In the second case the true state of affairs was early suspected and later definitely established; nevertheless, the signs of bronchial obstruction are interesting and the histologic features as demonstrated in the accompanying illustration furnish clear evidence as to the manner in which the bronchial wall may be invaded.

CASE II.—P. Z., aged forty-nine years, a white man, was admitted to the service of Dr. Thomas McCrae on February 13, 1928. He complained of cough, pain in the upper abdomen and middle of the back, and loss of weight. The family history was negative.

He had had good health except for a susceptibility to colds during the last

several years. He had pneumonia in 1922 from which he made a good recovery. The present illness began in November, 1927, at which time he was awakened one night with a sharp attack of pain in the epigastrium. He was not nauseated and did not vomit. He remained in bed for two weeks on a restricted diet and improved considerably. He then resumed work and continued until about two weeks before admission to the hospital at which time his pain returned. The pain came on about ten minutes after eating and lasted for about an hour or more. The pain was no longer restricted to the epigastrium but was likewise felt in the back.

During the last several weeks he had been increasingly distressed by cough and shortness of breath. He had lost 34 pounds in the last two and a half months.

Physical examination on admission to the hospital showed a fairly well-nourished patient with slight dyspnea, slight cyanosis and a tinge of grayish pallor. The sclerae were icteroid. There was marked infection of the gums. Examination of the throat and neck was negative.

Heart: The apex beat was not seen or felt but cardiac dullness seemed within normal limits. The sounds at the apex were distant but not abnormal.

Lungs: There was slightly lessened expansion at the left base. The percussion note anteriorly on the left was tympanitic, fremitus was decreased and breath sounds were almost entirely absent. Posteriorly the findings were the same. On the right side there were hyperresonance and exaggerated breath sounds.

Abdomen: There was rather marked tenderness and rigidity of the upper abdomen more marked on the right side and in the epigastrium. The spleen and the liver edge could not be felt although the liver seemed enlarged. The physical examination otherwise was negative.

The temperature was slightly subnormal; the pulse rate averaged 80; the respirations were slightly increased; and the blood pressure was within normal limits.

Within a week it was noted that the patient was losing ground rapidly and there was some evidence of jaundice which gradually deepened as time went on. Physical signs were not so pronounced over the left chest. There was some evidence that air was entering the lower lobe of the left lung and breath sounds could be heard a little better posteriorly. Rigidity of the upper abdomen became more marked. A tentative diagnosis was made of carcinoma in the upper abdomen, probably of the pancreas, with metastasis to mediastinal lymph nodes causing obstruction of the bronchus on the left side.

Laboratory studies other than the Roentgen ray gave no additional information.

The gastrointestinal studies (Dr. Leon Solis-Cohen) indicated possible carcinoma of the pancreas and Roentgen ray studies of the chest (Fig. 2) (Dr. John T. Farrell, Jr.) showed a distinct nodular enlargement at each root area. The masses were fairly sharply circumscribed and were thought to be due to the enlargement of the lymph nodes. There was a distinct difference in the aëration of the two sides of the chest, which was very pronounced on fluoroscopic study. It was noted that the right diaphragm moved freely while the left moved practically not at all, and with expiration the heart was displaced to the right. These changes indicated an obstructive emphysema of the left lung due probably to compression of the bronchi.

The patient rapidly grew worse and died on April 22, 1928.

Necropsy demonstrated a large primary carcinoma of the pancreas with metastasis to tracheobronchial lymph nodes. Near the bifurcation of the main bronchus of the left lung there was invasion of the bronchial wall (Figs. 3 and 4) producing marked stenosis.

The third case illustrates the second point mentioned in the introduction, that is, how confusion in diagnosis may be brought about by the extrathoracic metastases of primary bronchial carcinoma.

CASE III.—J. V., a white man, aged forty-seven years, was admitted to the service of Dr. Thomas McCrae, March 24, 1928. He complained of cough, expectoration, pain in the right chest, loss of weight and strength. The family history was negative. The patient stated that he had always enjoyed good health. He used tobacco and alcohol moderately. He had lost about 30 pounds in weight in the last five or six weeks.

The present illness began about five months before admission to the hospital with cough and expectoration. The expectoration at first white gradually increased in quantity and became yellowish. Occasionally the sputum was blood streaked. Later the patient vomited with the attacks of coughing. For a few days before admission he noted some swelling of his feet and ankles.

Physical examination on March 28 showed a very well-developed but poorly-nourished patient who was markedly dyspneic, and slightly cyanotic. There was no clubbing of fingers. The face and neck were rather red and this redness was increased by cough. The cervical lymph nodes on both sides were moderately enlarged. There seemed to be some fixation of the larynx but no tracheal tug. There was slight distention of the veins of the upper chest and a rather distinct costal fringe of capillaries. The heart was within normal limits and the sounds were normal.

The chest expansion was generally diminished but especially so on the right side. The percussion note on the right side was tympanitic with a sort of wooden tympany over the apex and in the first and second interspaces. The breath sounds were much diminished. On the left side the percussion note was hyperresonant and the breath sounds were exaggerated. Parasternal dullness seemed increased in the first and second interspaces on both sides. Posteriorly the findings were the same, that is, hyperresonance and exaggerated breath sounds on the left; tympany and absent breath sounds over the upper right chest and distant breath sounds over the lower right chest. Abdominal examination showed a large mass occupying the epigastrium both to the right and left of the umbilicus which seemed as though it might be connected with the liver. The remainder of the physical examination was negative.

A tentative diagnosis was made of abdominal new growth with metastasis to the mediastinum and neck, obstructive emphysema of the right upper lobe due to bronchial compression from lymph-node enlargement and probable secondary infection of the right lower lobe.

The temperature was 101° on admission, the pulse 110 and the respirations 32. The blood pressure was 135 systolic and 60 diastolic.

Roentgen ray examination of the chest (Fig. 5) showed an area of increased density in the middle portion of the right lung. There was marked thickening of the root shadows on the right side. The Roentgen ray interpretation was malignant metastasis with enlargement of mediastinal lymph nodes. The gastrointestinal tract showed no evidence of malignancy, and gall-bladder function as determined by the cholecystogram was normal. The van den Bergh test gave a slightly positive indirect reaction. The blood Wassermann was negative. The blood count was nearly normal. Repeated sputum examinations were positive for blood but failed to show tubercle bacilli. Urine studies were essentially negative.

Bronchoscopic examination by Dr. L. H. Clerf on March 31 revealed "marked compression of the lower end of the trachea; the carina was compressed from before backward, so that the anterior and posterior extremi-

ties were practically on the same plane and its edge could be seen only on deep inspiration. The orifices of both main bronchi, especially the right, were smaller than normal; the angle of bifurcation of the trachea was widened; the right main bronchus showed a definite stenosis, apparently the result of infiltration of the bronchial wall. There was considerable rigidity of the right bronchus and its lumen was triangular in appearance. The mucosa was intensely inflamed, granular, and bled slightly when touched. A moderate quantity of purulent secretion was aspirated from the right bronchus. The bronchoscopic diagnosis was compression stenosis of the trachea and right bronchus; widening of the angle of tracheal bifurcation. The bronchial findings suggested the presence of large tracheo-bronchial lymph nodes producing compression of the lower end of the trachea and infiltration of the right bronchus."

The patient grew worse rapidly and died on April 13 from pulmonary edema.

Necropsy showed a primary carcinoma of the right main bronchus producing marked constriction of its lumen. There was an abscess of the upper portion of the lower lobe about 3 cm. in diameter and an area of consolidation in the lower portion of this lobe. There was marked involvement of the mediastinal lymph nodes. The liver weighed 4100 gm., being the seat of numerous large metastatic nodules.

In this case huge enlargement of the liver due to metastases from a bronchial carcinoma misled me into believing that the primary new growth was in the abdomen and that the secondary lesion was in the lung.

In the fourth case we again suspected that an abdominal new growth had metastasized to the lung and in this instance although autopsy was not obtained the Roentgen ray of the chest quite definitely established the correctness of this view.

CASE IV.—S. G., aged forty years, an adult, white male, was admitted to the service of Dr. Thomas McCrae on March 1, 1928. He complained of shortness of breath; cough and expectoration; and pain on the right side of the abdomen. The past history revealed no serious illness apart from frequent sore throats. The present trouble began five weeks before admission to the hospital with an illness diagnosed as gripe. He had pain on the right side, cough, and later, expectoration and shortness of breath. He had been in bed off and on since that time. There had been very little loss of weight.

The physical examination on admission to the hospital showed a well-developed, well-nourished patient who was quite dyspneic and looked very ill. Examination of the chest showed general restriction of expansion, more marked on the right side. The percussion note on the right side was tympanitic above and impaired below, and over the area of tympany the breath sounds were diminished. The left side throughout was hyper-resonant and the breath sounds were exaggerated.

Examination of the abdomen showed a mass on the right side which roentgenologically did not seem to be connected with the gastrointestinal tract, nor did it seem connected with the liver. It was thought that it probably arose from the right kidney and a tentative diagnosis of probable hypernephroma was made although blood never was found in the urine. The chest signs were interpreted as due to metastasis from this abdominal new growth and the Roentgen ray confirmed this opinion (Fig. 6).

The patient died at home the following month and no autopsy was obtained.

Comment. Among the many difficulties encountered in the diagnosis of primary carcinoma of the bronchi the domination of the clinical picture by an abscess of the lung peripheral to the new growth deserves prominent mention. Another difficulty spoken of by various authors concerns metastases from a small primary bronchial carcinoma to other organs producing striking manifestations of disease in these other organs and thus obscuring the diagnosis of the primary new growth. A third important diagnostic consideration works in exactly the opposite manner. Metastases from extrathoracic new growths to the parenchyma of the lungs have long been known and increasingly recognized with the wider use of the Roentgen ray. Little attention has been paid, however, to the metastases from extrathoracic new growths to tracheobronchial lymph nodes causing enlargement of these nodes, compression of the bronchi and in this manner producing signs and symptoms of pulmonary disease. Under such circumstances, the evidences of pulmonary disease may dominate the clinical picture, and lead one to believe that the primary new growth is bronchial in origin.

Bronchial compression brought about by enlargement of peribronchial lymph nodes is capable of producing an obstructive emphysema as shown in accompanying plate from Case II.

Obstructive emphysema of foreign body origin is well known, particularly in children and usually is readily recognized. Here ball-valve action of the foreign body in the bronchus permits air to enter a portion of the lung but does not allow it to leave, and in this manner varying grades of overdistention of the lung are produced. Bronchial compression brought about by pressure of large lymph nodes probably acts in a somewhat similar manner. It would seem that air enters the partially closed bronchus successfully but due to narrowing of the bronchus on expiration finds difficulty in leaving and that portion of the lung supplied by the partially obstructed bronchus remains overdistended for a varying period of time. When complete closure of the bronchus occurs the air from that portion of the lung is absorbed and atelectasis results.

The signs of obstructive emphysema are usually distinctive. There are deficient expansion, tympanitic percussion note and diminished or absent breath sounds over the affected area. The signs may vary from time to time as influenced by rest, by progression of the bronchial compression, or by retained secretions. It is important to remember that over the unaffected lung one is apt to obtain hyperresonance and exaggerated breath sounds due to the compensatory overexpansion. For this reason, the error has been made of considering a lesion to exist on the sound side.

The necessity for differentiation from pneumothorax or collapse of the lung may arise. In pneumothorax as in obstructive emphysema one may obtain a tympanitic percussion note and diminished or absent breath sounds over the affected area, and the displacement phenomena of pneumothorax may not be sufficiently pronounced

to be of aid in diagnosis. One is not so apt to be confused by collapse of the lung, as here one usually obtains a dull percussion note over the affected area and the displacement of the heart toward the involved side is an important and usually a striking feature of the condition. Other findings such as a positive coin test in pneumothorax and the febrile reaction of collapse together with the history and the evidence disclosed by the Roentgen ray will probably be sufficient for ready differentiation.

Conclusion. There is often considerable difficulty in differentiating primary and secondary carcinoma of the bronchi for the reason that extrathoracic new growths may metastasize to and cause enlargement of tracheobronchial lymph nodes, producing bronchial compression, so that chest symptoms and signs dominate the clinical picture. These secondary growths may actually invade the bronchial wall in such a manner that bronchoscopist and microscopist likewise may be confused with regard to the point of origin of the new growth.

It is important to differentiate primary and secondary carcinoma of the bronchi because early recognition and prompt treatment of primary bronchial carcinoma offers some hope from the standpoint of improvement and possible cure.

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SPONTANEOUS NONRHYTHMIC VARIATIONS IN THE BLOOD-PRESSURE LEVELS AND IN THE "SILENT GAP."

A THEORY OF VASOMOTOR ARRHYTHMIA.

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THAT blood pressure occasionally undergoes spontaneous variations without any detectable cause was known for a long time. Janeway¹ mentioned four forms of variations that occur in experimental animals—more rapid, cardiac; larger, respiratory; longer and slighter, Traube-Hering and spontaneous nonrhythmical variations, which may be reflex or due to change in the central nervous system. He added that these periodic variations are evident in the human as well as in animals, but doubted if such variations are ever higher than 30 mm. of mercury.

No reference could be found in the literature, however, of the extent and nature of spontaneity in blood-pressure variations and

its possible explanation and significance. In an attempt to determine these factors, I made a study of 100 patients, 72 of whom had normal or subnormal pressures and 28 hypertensives. The method of procedure was to have the patient in a dorsal recumbent posture, head and upper part of the body somewhat elevated by support, such as that offered by the ordinary Isaacs table, to give more comfort and rest. The examining room was isolated from any outside disturbances, as far as possible, and the patient was allowed to remain at rest for three to five minutes before determinations began. The pulse rate was then taken the first fifteen seconds and the systolic and diastolic readings during the rest of the minute, determinations being made every minute for periods of ten to twenty-five minutes. Each patient's readings were tabulated in order, the pulse rate per minute having been determined by multiplying the rate in fifteen seconds by four.

Of the 72 patients with normal or subnormal blood pressures, 50 showed practically no variations in the pressure levels or only such slight variations as would be explained by respiratory activity. Nineteen showed variations of 10 to 20 mm. and 3 of more than 20 mm., but not higher than 30 mm. Of the 28 hypertensive patients, on the other hand, 12 showed variations of 10 to 20 mm., 13 of 20 to 30 mm. and 3 of 40 mm. or higher. In some cases the systolic pressure level fluctuated most, in others the diastolic, as shown in Table and Fig. 1.

TABLE I.—FLUCTUATIONS IN BLOOD PRESSURE OF A FEMALE WITH PRESSURE WITHIN NORMAL LIMITS.

Minute.	Pulse rate.	Blood pressure.	
		Systolic.	Diastolic.
1	80	124	96
2	80	126	102
3	70	120	78
4	80	130	90
5	80	122	90
6	78	128	90
7	80	122	94
8	78	120	86
9	74	116	88
10	72	120	90
11	80	118	90
12	80	120	90
13	78	120	96
14	72	118	96
15	76	118	92
16	76	123	90
17	76	122	88
18	76	118	86

These readings were obtained from a female, aged twenty-seven years, whose blood pressure was within normal limits. Her complaints were shifting body pains, slight shortness of breath on walking two flights of stairs and constipation. She was obese, weight being 173 pounds, height 62 inches. Her heart and lungs

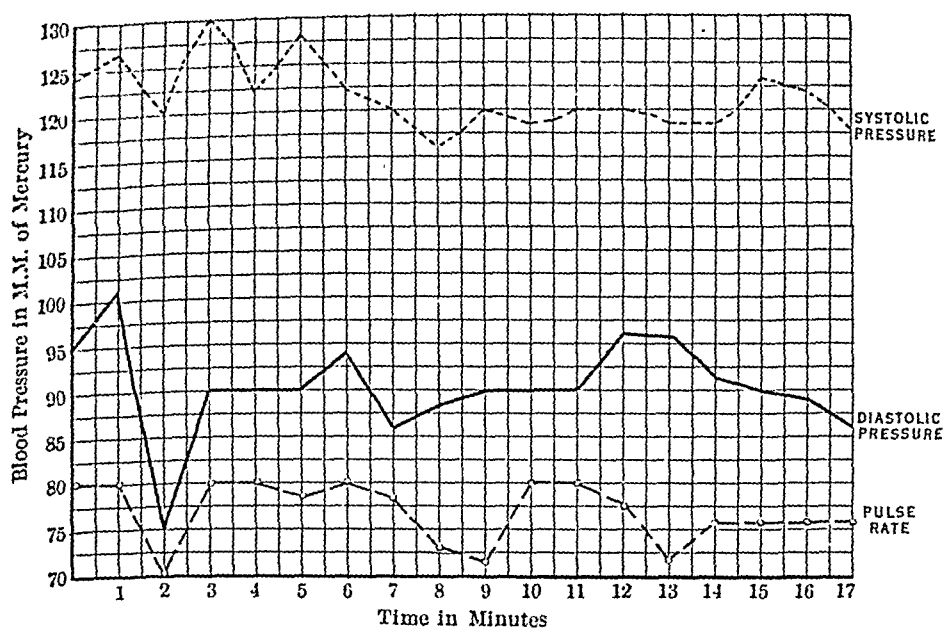


FIG. 1.

were negative. She had chronically infected tonsils with a history of repeated attacks of tonsillitis. The difference between her maximum and minimum systolic readings was 14 mm., while that of the diastolic was 24 mm. The pulse pressure was 22 to 45, comparing extremes. There is a disproportion in the fall and rise of the pressure levels.

TABLE II.—FLUCTUATION IN BLOOD PRESSURE IN HYPERTENSION.

Minute.	Pulse rate.	Blood pressure.	
		Systolic.	Diastolic.
1	84	184	120
2	84	164	124
3	76	170	128
4	80	204	120
5	76	210	120
6	80	204	114
7	80	160	110
8	72	200	118
9	74	210	120
10	72	204	130
11	76	204	120
12	76	210	120
13	74	190	128
14	74	210	116
15	76	200	120
16	74	206	120
17	76	200	100
18	76	204	130
19	74	204	120
20	72	204	140
21	72	212	140
22	72	200	120
23	70	204	150
24	72	204	120
25	76	194	112

In the hypertensive the fluctuations seem to vary with the type of hypertension. The individual presenting periodic changes in blood pressure, as described in a previous paper,² seems to show greater fluctuations than the one whose pressure is permanently high. This is shown in Fig. 2 and Table 2 obtained from a female,

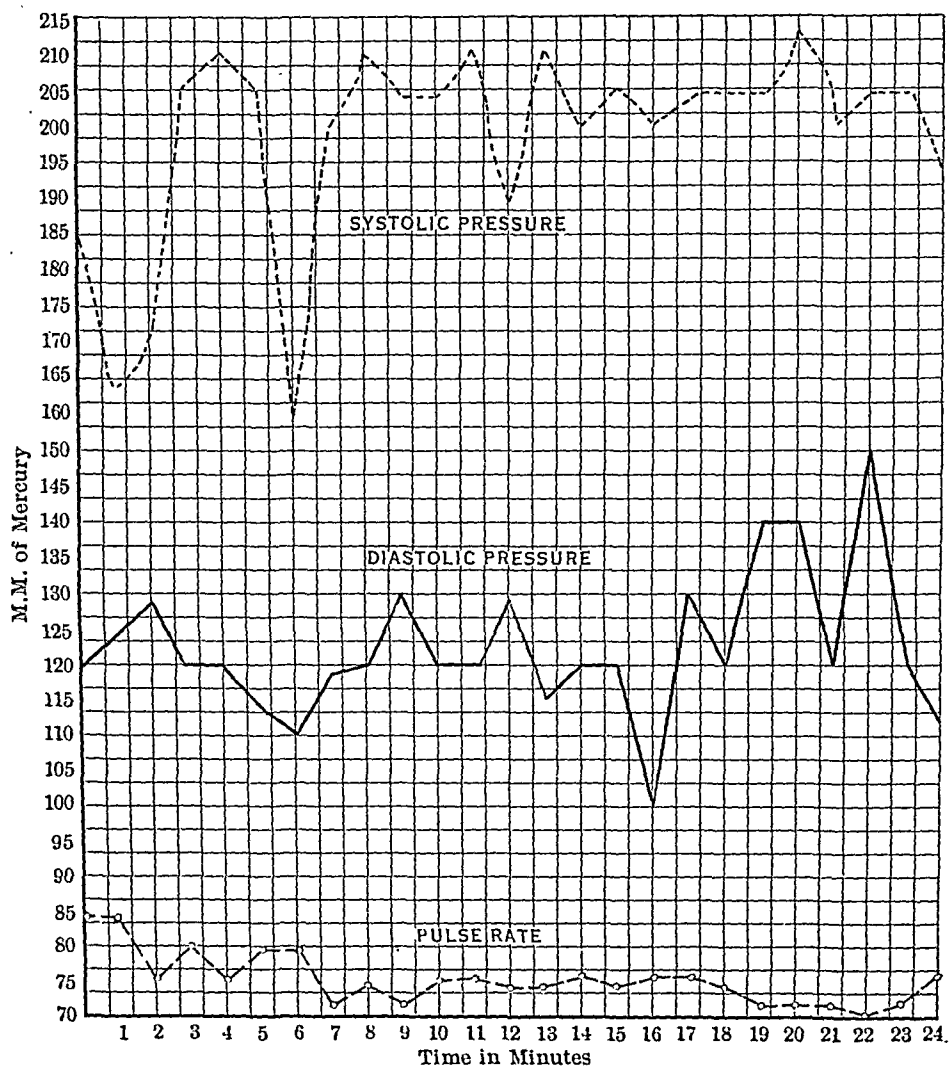


FIG. 2.

aged fifty-eight years, who, aside from vague aches and pains, felt well. She presented hypertension with marked periodic remissions. As is noticed, her systolic pressure level shows marked fluctuations the first eight minutes and lesser ones during the rest of the observation. The diastolic level shows greater fluctuations the latter part of the observation. There is no correspondence between the systolic and diastolic curves. The maximum systolic reading is 212 mm. and the minimum 160 mm., making a difference of 52 mm. The maximum diastolic reading is 150 mm. and the minimum 100 mm., making a difference of 50 mm. The pulse pressure, is as low as

50 mm. at the sixth minute and as high as 100 mm. at the sixteenth minute.

TABLE III.—SIMILAR FLUCTUATIONS IN A HYPERTENSIVE ON TWO OCCASIONS.

Minute.	Blood pressure.			
	Systolic.		Diastolic.	
	8/10/27	9/17/27	8/10/27	9/17/27
1	178	180	104	110
2	150	195	90	100
3	154	194	92	100
4	152	198	96	96
5	154	190	90	94
6	176	186	90	98
7	168	190	92	96
8	180	186	94	96
9	178	190	90	100
10	168	168	96	100
11	175	174	98	
12	158	...	92	
13	180	...	94	
14	180	...	90	
15	158	...	90	
16	164	...	98	

An interesting feature observed in two hypertensive cases is that the extent of fluctuations was the same on two different occasions in the same individual, under varying levels of blood pressure. The findings of 1 of these cases are shown in Fig. 3 and Table 3, obtained

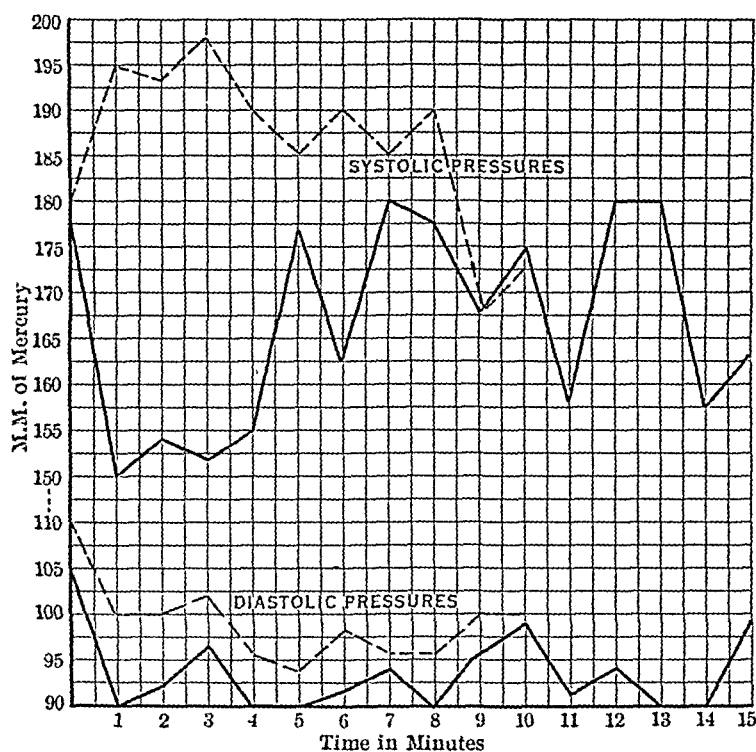


FIG. 3.—Heavy lines represent blood pressure on August 10, 1927. Broken lines represent blood pressure on September 17, 1927.

from a female, aged fifty-seven years, who was mildly diabetic and hypertensive. Aside from some pain in the right shoulder, she had no other complaints. Her blood pressure on August 10, 1927, was maximum systolic 180 mm. and minimum 150 mm., making a difference of 30 mm. The maximum diastolic was 104 mm. and minimum 90 mm., making a difference of 14 mm. On September 17 the maximum systolic was 198 mm. and minimum 168 mm., making a difference also of 30 mm., while the maximum diastolic was 110 mm. and minimum 94 mm., making a difference of 16 mm.

In the chronic hypertensive individual, whose blood pressure is persistently high and who shows definite anatomic, cardiovascular changes, the fluctuations are comparatively slight. This is illustrated in Fig. 4 and Table 4, representing the findings of a male, aged fifty-five years, who for the past ten years was known to have had hypertension. He developed a sudden left hemiplegia two years ago, of mild degree, lasting two days. His chief complaints were precordial pain on exertion, moderate dyspnea and frequent pain in the back of his head and neck. He was obese, markedly arteriosclerotic, with some exophthalmos and edema of the lids. His heart was greatly hypertrophied and the aortic arch was found to be markedly widened under the fluoroscope. The heart sounds were strong, booming, with accentuation of the aortic second sound. No murmurs were heard. His urine and blood chemistry examinations were negative, as was the blood Wassermann test. He died from cerebral hemorrhage.

TABLE IV.—SLIGHT FLUCTUATIONS IN A CHRONIC HYPERTENSIVE.

Minute.	Blood pressure.			
	Systolic.	Limits of gap.		Diastolic.
1	220	195	180	130
2	220	215	190	120
3	220	195	175	120
4	218	208	170	130
5	208	200	180	130
6	224	200	174	120
7	208	190	160	120
8	214	210	180	130
9	215	205	170	125
10	210	200	180	125
11	220	190	W. 170	130
12	215	190	160	130
13	205	190	170	130
14	210	190	W. 170	130
15	210	190	170	130

This patient showed a "silent gap" in his blood pressure—a term designating the temporary disappearance of the sounds heard during the course of auscultatory examination of the blood pressure. It is

elicited by the gradual deflation of the air bag and carefully listening for the appearance of the regular, rhythmic sounds indicating the systolic blood-pressure level. On further gradual lowering of the pressure in the bag, the sounds are found to disappear for a certain number of millimeters, only to return again and persist until the permanent diastolic disappearance of the sounds occurs. For example, assuming that the systolic level is found to be at 180 mm.,

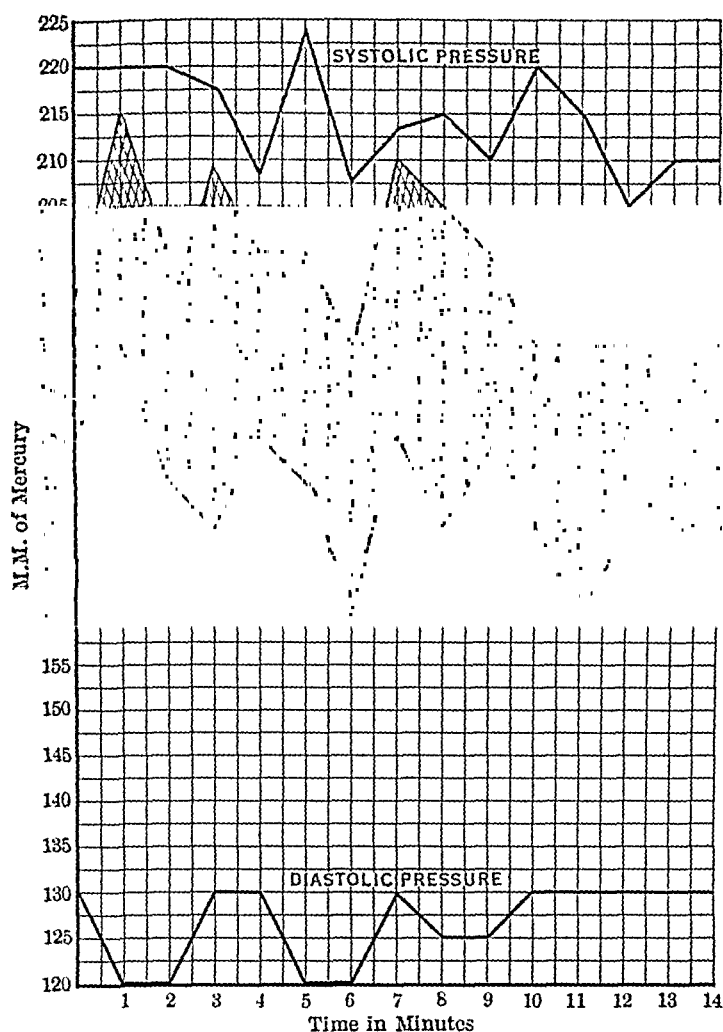


FIG. 4.

the sounds will continue to be heard for several millimeters, say down to 170, when they will disappear for a varying number of millimeters, say down to 150, after which they will be heard again to the true diastolic level, say of 100 mm. The length of time for the disappearance of the sounds varies in different cases.

The condition was first described, according to Gibson,³ by the French writer, Tixier, who thought it to be present only in some

cases of mitral stenosis. Gallavardin, according to the same author, named the phenomenon "trou auscultoire," and stated that he met it in other conditions than in mitral stenosis. I first observed this phenomenon in a case of aortic insufficiency at the cardiac clinic of the New York Post Graduate Hospital, before I knew of its existence from the literature, and thereafter watched for it in all cases in which blood-pressure determinations were done for any length of time. I found the condition to be comparatively rare, and to occur occasionally in the hypertensive individual, particularly in the chronic and graver form. I also found that just as the systolic and diastolic levels may fluctuate, so may the upper and lower limits of the gap.

This is well illustrated in the figure and table of findings of the patient under discussion. As will be seen, the systolic and diastolic levels fluctuate comparatively little, while the fluctuations of the gap are more marked. The maximum and minimum limits of the gap are 215 mm. and 160 mm. respectively, at an interval of five minutes. The nearest interval between the systolic level and the upper gap level in the same interval of time is 4 mm. in the seventh minute, and the farthest is 30 mm. in the tenth minute. Here, however, as in the thirteenth and fourteenth minutes, there is no complete gap in the sound, but a weak sound (W) could be heard, continuous from the systolic beginning to the diastolic end. The lower level of the gap is further from the true diastolic pressure than the upper is from the systolic. Thus, in the first minute it is as long as 70 mm., while in the eleventh minute it is 30 mm.

TABLE V.—OCCURRENCE OF THE SILENT GAP.

Minute.	Blood pressure.			
	Systolic.		Diastolic.	
1	190	140
2	190	145
3	180	145
4	190	142
5	206	140
6	210	200	160	140
7	220	200	160	140
8	220	150
9	220	200	175	140
10	220	200	160	140
11	220	200	150	140

Another peculiarity observed about the gap is that it may occasionally occur for two or more successive minutes or even in isolated

determinations, disappear and reappear again. This is shown in Fig. 5, and Table 5, obtained from a female, aged twenty-eight years, suffering from chronic pyelonephritis of four years' standing. The condition followed pregnancy which was associated in the sixth month by uremic manifestations and spontaneous delivery. She was unconscious at that time for four days, following repeated convulsions. Since then her condition has been that of recurring semi-invalidism. Pus, albumin, various forms of casts are constant urinary findings, and the blood pressure ranges between 180 and 220 mm. systolic and 140 to 150 mm. diastolic. As will be noticed from the figures, there was no gap the first four minutes, during

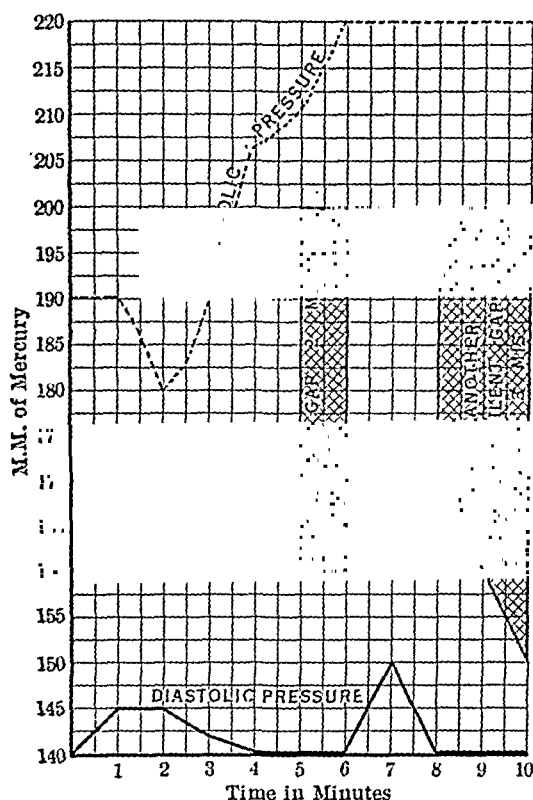


FIG. 5

which time the systolic blood pressure ranged between 180 and 205 mm. At the fifth minute the systolic pressure mounted to 210 mm., with a gap appearing between 200 and 160 mm. At the sixth minute the systolic level rose to 220 mm., the gap remaining the same. During the seventh minute no gap was present, and the diastolic level was higher. In the last three minutes there were no fluctuations in either the systolic or diastolic levels, but the gap gradually grew larger.

Discussion.—The important facts to be considered in the observations presented in this paper are: (1) That in some individuals

with normal blood pressures the systolic and diastolic levels fluctuate apparently spontaneously; (2) that in the hypertensive individual showing periodic remissions such fluctuations are the rule and are very prominent; (3) that in the chronic, nonremittent form of hypertension in which anatomic cardiovascular changes are marked, the fluctuations are less prominent, but a silent gap in the sounds may occur; (4) that every level of blood-pressure reading fluctuates independently of the other and in a disorderly fashion; (5) that the extent of the fluctuations seems to be approximately the same on different occasions, even if the blood-pressure readings are not the same.

Physiologic Considerations. In an attempt to explain these phenomena, a brief consideration of the mechanism of blood-pressure production and maintenance is necessary.

The factors concerned in this mechanism are the heart energy, the elasticity of the vessel walls, the volume of circulating blood and the peripheral resistance. Of these, the peripheral resistance is the dominant factor in initiating *changes* in blood pressure when the person is physically at rest. Exceptions are when variations in the heart activity occur, such as is found in auricular fibrillation and pulsus alternans. Also such results may follow deep breathing with its mechanical effect of thoracic aspiration and reflex vasomotor effect, as has been shown by some investigators, such as Erlanger and Festerling⁴ and Lewis.⁵ Such conditions are, however, excluded from our discussion.

The greatest factor in the production of peripheral resistance is tonus of the vessel walls, for though the resistance produced by the branching of the arteries and by internal friction due to the viscosity of the blood are also factors, such are negligible from a variability viewpoint. It is the constant change in the tonus of the arteries, arterioles and capillaries, especially in the splanchnic circulation, that produces its changing effect on the general blood pressure. Such tonus is maintained by the vasoconstrictor nerves, having their main center in the medulla and some subsidiary centers in the spinal cord. Increased activity of the center produces vasoconstriction with a rise in pressure, decreased activity produces vasodilation with a fall.

Under various states of emotional and physical activity such increase or decrease is produced by an increase or a decrease in the impulses reaching the center through various afferent channels. In conditions of rest, such as in our observations, any variation in activity of the vasoconstrictor nerves must be due either to spontaneous variations in activity of the vasomotor center or of the efferent vasoconstrictor nerves or of both. In other words, we must assume here the existence of an automaticity in the vasoconstrictor nervous mechanism which undergoes constant spontaneous changes independent of any change in the extrinsic nervous influences, the

extent of which varies with the individual. In most normal persons there is a stability of this mechanism with an established level of tonicity, yielding little variation, except reflexly. In some cases, however, there seems to be more or less fluctuation in this vasomotor tone, nonrhythmic in nature, to which the name "vasomotor arrhythmia" may be applied, and to which the physiologic homologue of sinus arrhythmia can be compared. Like the latter, which was shown by Mosler⁶ to have no periodicity in its variations nor constant relationship to the rhythm of respiration, this arrhythmia is similarly characterized. It seems to be most pronounced in some of the benign hypertensive individuals.

As to the underlying cause of this arrhythmia, nothing but conjectural assumptions can be made. We may assume a lability of the vasomotor center in the medulla caused by some chemical substance, metabolic or toxic, which produces various grades of stimulation and depression from moment to moment. It is more likely however, that local variations in the blood supply to the medulla from moment to moment, such as would be caused by local vascular spasm, may be the underlying factor. It is a long-recognized physiologic law that diminished blood supply to the medulla results in a compensatory rise in the systemic blood pressure. This has been proved by Starling, who suggested claudication of the center vessels as a cause of hypertension. Cushing⁷ proved the effect of cerebral anemia on rise in the systemic blood pressure by his experiments in cerebral compression and decompression on animals and in some of his clinical cases. Boardley and Baker⁸ investigated the arterial changes in the medulla in 14 cases of arteriosclerosis with hypertension and in 10 cases of arteriosclerosis without hypertension and found that in the hypertensive the medullary blood vessels were invariably involved in sclerotic changes while in the others they were not.

We may infer from these facts that in certain individuals there is a local vasospasm of the vessels of the medulla producing some anemia of the vasomotor center with a resulting rise in the general systemic blood pressure. This rise results in an increased blood supply to the center, producing a fall, soon to rise again when the fall is sufficient to produce more or less anemia of the center. This process is apparently continuous and occurs independent of any reflex condition.

The explanation of the "silent gap" encountered in some individuals is difficult. It may perhaps correspond to the fifth phase, or the so-called "phase of friction sound" of Brooks and Bleile,⁹ representing the period during which the blood passes through a slit-like opening of the partially compressed artery. How the sounds disappear is hard to understand.

Value of the Observations. The practical value of the observations presented in this paper is twofold: (1) It will teach us to avoid

the formation of too hasty conclusions in the observation and treatment of blood-pressure abnormalities; (2) it may throw some light on the causation of hypertension.

The first factor is appreciated when we realize how often conclusions are drawn from an occasional observation on the results of treatment or of environmental changes, producing presumably a drop in blood pressure. We only have to refer to the conflicting results reported by various observers on the effect of change in posture, for instance, on blood pressure or of certain drugs and methods in the treatment of hypertension, to see that spontaneity in blood-pressure changes is probably the underlying cause of such differences. To evaluate properly any method, a knowledge of the individual "normal" fluctuations must be had first. Only then can we judge if any change is due to the method.

Of greater value in the appreciation of these fluctuations is the possibility of associating them with the causation of hypertension, thus paving our way for a better understanding of that phenomenon. In view of the greater frequency and prominence of the occurrence of fluctuations in the benign hypertensive individual, we may conceive of vasomotor arrhythmia as being the cause of hypertension. Further observations will probably reveal the following stages in the development of the persistent form of hypertension: First stage, that of comparatively mild fluctuations seen in individuals presenting normal blood pressures. Second stage, that of greater fluctuations with an occasional rise above normal limits. Third stage, when the adaptations of the blood supply to the medullary vasomotor center becomes poor, due to increased spastic state and to some sclerotic changes of the vessels there, producing more prolonged periods of hypertension. Fourth stage, when as a result of the hyperactivity of the medullary blood vessels, marked sclerosis of these vessels has taken place, resulting in a permanent anemic state of the vasomotor center, with the resultant permanently high blood pressure, with comparatively slight fluctuations. The cases presented in this paper illustrate this conception fairly well, and it remains to be shown if those individuals with normal blood-pressure readings who show such fluctuations are the ones that will eventually develop hypertension, I am inclined to believe that such will be found to be the case.

Summary. A study of the pulse rate and blood pressure of 100 patients was made at minute intervals, for periods of ten to twenty-five minutes. Of 72 patients with normal blood pressure, 50 showed practically no fluctuations in their readings from minute to minute, 19 showed variations of 10 to 20 mm. and 3 of over 20 mm., but not higher than 30 mm. Of 28 hypertensive cases, 12 showed variations of 10 to 20 mm., 13 of 20 to 30 mm. and 3 of 40 mm. or higher. The greatest fluctuations occurred in hypertensive individuals showing periodic remissions. In some of the severe hypertensive cases a

"silent gap" in the sounds was found, the levels of which showed independent fluctuations.

A theory of "vasomotor arrhythmia" is offered to explain this phenomenon. The theory assumes a disturbance in the discharge of rhythmic vasomotor impulses from the medullary vasomotor center, caused by local anemia there, such as would be produced by angiospasm or the like.

Based on these findings, the pathogenesis of hypertension is suggested as occurring in four stages: (1) In an instability of the normal blood pressure; (2) in an occasional rise of the pressure to above normal levels; (3) a more frequent occurrence of hypertension, with deeper fluctuations of blood-pressure levels, as a result of some added structural vascular changes in the medulla to those of functional changes; (4) the production of definite anatomic changes in the vessels of the medulla, resulting in more or less permanent rise in blood pressure, with smaller fluctuations.

Conclusions. Certain individuals have persistent fluctuations in their blood-pressure levels even under conditions of rest. Such fluctuations are most prominent in hypertensive individuals showing periodic variations, but occur also to a less extent in all other hypertensive cases, and in some cases with normal blood pressure. Because of its constant occurrence in hypertensive cases, and its occasional presence in normal blood-pressure cases, we may consider such latter cases as heading toward hypertension. To explain persistent fluctuations in pressure, we must assume a disturbance in the rhythmic vasomotor discharges that normally maintain the blood pressure at a constant level when the person is at rest, and a sort of "vasomotor arrhythmia" to set in. The recognition of the existence of such "normal" fluctuations will avoid the mistaken belief in the potency of some therapeutic factors, or in the efficiency of some blood-pressure tests.

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ACUTE MASSIVE (NONSURGICAL, NONTRAUMATIC) PULMONARY ATELECTASIS.

REPORT OF TWO CASES.

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SINCE 1890, when Pasteur first described pulmonary atelectasis, which he found in association with postdiphtheritic paralysis of the diaphragm, it has been described by other observers in association with various disturbances, largely following surgery or traumatism.

Although internists have seen and recognized this condition as a definite clinical entity in surgical patients, it would appear from the literature that, except to state that it occurs in purely medical conditions, relatively few have described its actual occurrence.

Pasteur, in 1914, reported 16 cases of massive collapse in a series of 201 postoperative complications. Jackson and Lee¹ state that 48 cases have been recorded in the literature since Pasteur's observations in 1914, that Scott in January, 1915, had collected 64 cases and reports that he had access to 12 unpublished records of cases. Norris and Landis² state that massive collapse of the lung occurs as a complication of pneumonia. Rose Bradford³ reports an autopsy of such a case. Tidy⁴ reports a doubted case of massive collapse of the entire right lung in the case of diaphragmatic pleurisy. Chevalier Jackson⁵ reports a very large experience with collapse of a part or of the entire lung as a result of the lodgment of foreign bodies in the bronchi. Pasteur saw lobar collapse of bases of the lung in pleurisy, apical pneumonia and hydrochloric acid poisoning. Collapse of the lung was reported by N. Kletz⁶ complicating an attack of acute meningitis. Massive collapse complicating a case of abscess of the lung was reported by Elwyn.⁷ Regan⁸ records a case of collapse of lung in a case of acute poliomyelitis. Wallgren⁹ found collapse of the lung in 8 cases of pneumonia in children, with displacement of the heart toward the affected side, all of which recovered. Gwyn¹⁰ states that collapse of the lung was diagnosed in 3 cases; 2 suffered from lobar pneumonia and 1 from a respiratory infection, in all probability also pneumonia.

Etiology. Different theories as to its cause have been advanced but none has met with general approval. Jackson and Lee,¹¹ after a careful analysis of many diverse conditions with which massive collapse is associated, show two factors to be constant; (1) obstruction of the bronchial tree, which is followed by the absorption by the pulmonary circulation of the air imprisoned in the alveolar tissue distal to the obstruction; (2) some interference with the respira-

atory movements. This interference may be partial or complete but always results in decreased aëration of the pulmonary tissue on the involved side.

Scott¹² believes that spasm of the bronchiole, or a vasomotor disturbance resulting in the swelling of mucous membrane similar to angioneurotic edema are possibilities in causing massive collapse of the lung. Until more direct evidence of the cause and effect are produced, the theory of bronchial obstruction with some interference in respiratory movement seems most plausible.

Autopsy performed upon patients showing massive collapse of the lung at times fails to show mechanical obstruction of the bronchial tree. It must be borne in mind that considerable rough handling and twisting of the lungs takes place in the course of their removal from the body, and may readily dislodge the obstruction. Pulmonary edema, labored breathing with cough often occurring for a varying number of hours before death, may be factors in dislodging obstructions of the bronchi by mucus or secretions acting as plugs.

Jackson states that following the removal of a foreign body from the bronchus the lung becomes air-containing slowly, usually twelve to forty-eight hours elapsing before it becomes fully expanded. He also finds that when a new growth in the bronchus completely occludes the entrance of air to that lung, pulmonary atelectasis occurs. Removal of the tumor allows air to reënter and the lung expands.

Lee, Tucker and Clerf,¹³ from the 30 cases of postoperative massive atelectasis whose records they have been able to study, are persuaded that two factors have been constant in practically all in this group: (1) a thick, viscid bronchial secretion, and (2) some inhibition of coughing. Because of the thick, tenacious character of this bronchial secretion and the inability or disinclination of the patient to clear it from the bronchi, it accumulates in the dependent portion of the bronchial tree until, at some point or points this stream of mucus completely occludes the lumen. These observers report the production of atelectasis of lungs in dogs after an injection into the bronchus of material removed from a patient suffering from this condition.

Lee, Tucker, Ravdin and Pendergrass¹⁴ state that the use of material removed from a clinical case to produce pulmonary atelectasis had not been reported prior to the work of Lee, Tucker and Clerf. They believe that the failure to reproduce this condition has been due to the inability to control the cough reflex. Their experiments consisted of preparing a solution of acacia, giving a dog a general anesthetic, preceded by hypodermic injection of morphin and perforating an exploratory laparotomy following which sodium amytol was given intraperitoneally to inhibit the cough reflex. Roentgen ray examinations of the chest made before and

after the introduction of the acacia solution into the bronchus by means of a bronchoscope and again following its aspiration from the bronchus showed that when the cough reflex was abolished atelectasis of the lung was produced and that the removal of the acacia solution by bronchoscopic aspiration caused the lung to reëxpand.

Symptoms. On account of the symptom complex differing from all others present in pulmonary disturbances, it is most important to be fully informed as to the symptomatology.

The condition is usually sudden in onset. Dyspnea and cyanosis are obvious upon inspection. The patient is usually not toxic and recovers in from two to four weeks. Associated conditions may cause toxemia and death. There is a very definite and sudden increase in the respiratory rate reaching up to 40 or 50 a minute. Fever ranging from 100° to 104° F. accompanies the condition. The polymorphonuclear leukocytes are increased, ranging from 10,000 to 20,000. The cough may be short, hacking and nonproductive early, later becoming productive in character. In one of our patients, the cough began immediately after the onset of the collapse and for a week the sputum was blood tinged.

The dyspnea, cough and cyanosis may cause the patient, who, though not toxic, to appear ill. His expression denotes anxiety. Bronchopneumonia may complicate collapse of the lung. It is believed that bronchopneumonia frequently develops in collapsed areas of the lung following surgical operations.

Physical Signs. A lobule, lobe or entire lung may be involved and occasionally the condition is bilateral. The lung area may alternate in collapse and expansion over a period of a week before clearing up entirely. The right lung appears to be involved three times more frequently than the left.

The examination of the chest shows diminution of, or even absent respiratory movements over the affected lung. The chest wall over the massive atelectasis presents a flattened appearance. The intercostal spaces are narrowed and depressed. The percussion note over the collapsed lung may be dull, due to the lack of air in the lung. This is usually posterior, occasionally it may be anterior. The part of the thoracic cavity not occupied by lung tissue due to collapse may be tympanitic, though more frequently it is hyperresonant. If the collapse is on the right side, the high position of the diaphragm with the upward displacement of the liver is most striking. Collapse of the right lung with the high diaphragm and liver flatness may be incorrectly diagnosed as a pleural effusion. Vocal fremitus is usually diminished or absent; rarely it is increased.

The quality of the breath sounds varies greatly. They are more often suppressed though occasionally are distinctly bronchial. Vocal resonance is absent or diminished over the collapsed lung in the cases with diminished breath sounds. Increased vocal resonance with bronchial breathing is present in the less frequent number of

cases. Over the thoracic cavity unoccupied by lung tissue, the breath sounds and vocal resonance are greatly diminished or absent. Râles, if present, are noted early in the condition or later as the collapse subsides. The râles are more likely to be coarse and of the musical type.

The unaffected lung usually presents an increased range of respiratory movements and a hyperresonant percussion note with exaggerated breath sounds. Large râles may be heard over this lung.

Displacement of the heart and mediastinum toward the affected side is usually the deciding factor in making the diagnosis. Without the displacement of the heart, the condition cannot be diagnosed with certainty by physical examination alone. In pulmonary atelectasis involving lobules of the lung, at times it is necessary to verify the clinical findings by Roentgen ray examinations.

The difference in the physical sign in the lungs is due to the degree of patency of the bronchi and the part of bronchial tree involved. When considerable air enters the bronchi, there is an increase in the intensity of the breath sounds and they are tubular in quality and in character. The signs with dullness suggest pneumonic consolidation.

The Roentgen ray is valuable in confirming physical findings especially in doubtful cases. The displacement of the heart toward the affected side is diagnostic.

Diagnosis. The diagnosis is made on the history of a nontoxic pulmonary condition sudden in onset, accompanied by cyanosis, cough, an increased respiratory rate, fever, increased pulse rate and the physical signs as described. The presence of a displaced heart and mediastinum toward the affected side with elevation of the dome of the diaphragm, verified by Roentgen ray examination, confirms the diagnosis of collapse of the lung.

Differential Diagnosis. The condition must be differentiated from pleurisy, with or without effusion, pneumothorax, pneumonia, pulmonary infarct or thrombosis, diaphragmatic hernia and acute dilatation of heart. Because the signs in collapse of the lungs closely simulate pneumonia, doubtlessly many cases of collapse are erroneously so diagnosed. The differential diagnosis from conditions resembling it is made by recognizing that in acute massive collapse of the lung the chest is immobile on the affected side with retracted interspaces, the diaphragmatic and cardiac encroachment on the affected side are extreme and the general symptoms are invariably less severe than in other acute pulmonary conditions with equally extensive physical signs. The absence of the toxic symptoms in collapse of the lung is most striking when compared with pneumonic infection.

Prognosis. The prognosis is good and any unfavorable results are believed to be due to the condition with which collapse is associated and not to the collapse itself. The prognosis is less favorable if

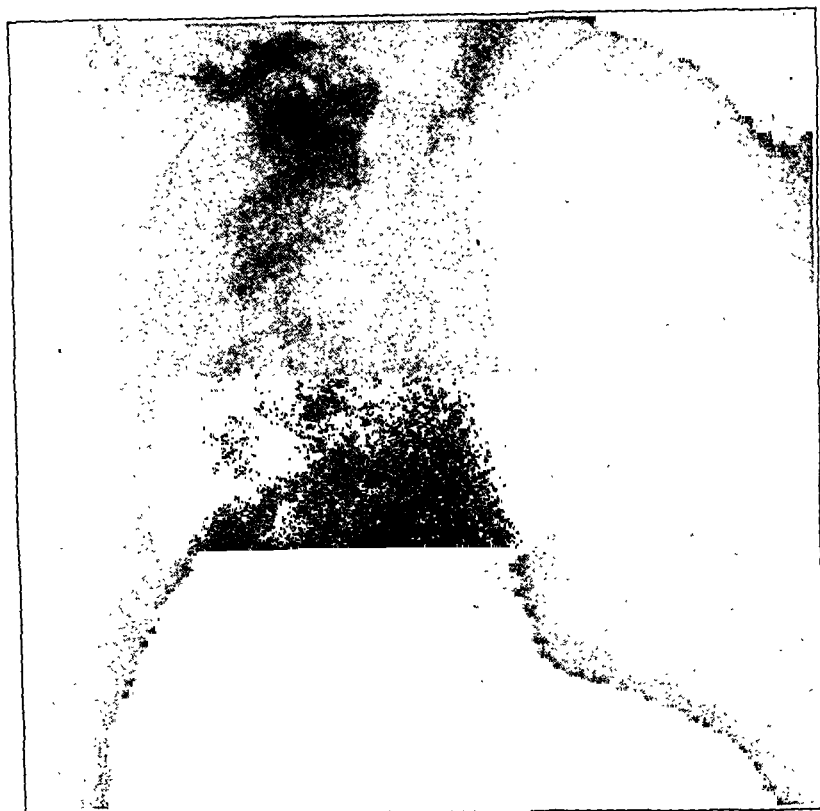


FIG. 1.—Roentgen ray photograph showing massive atelectasis of right lung with heart and trachea displaced toward the right.

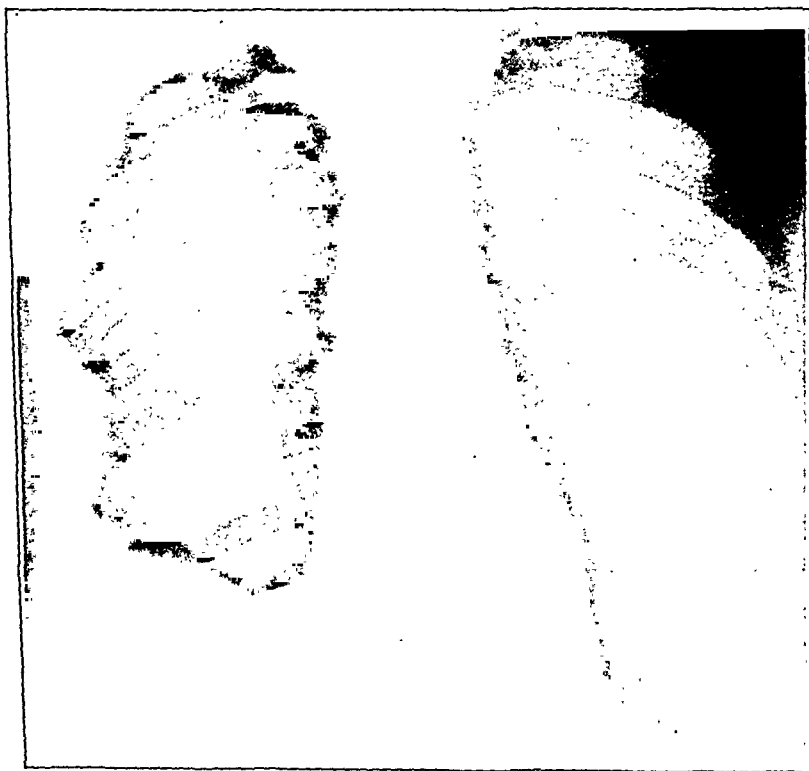


FIG. 2.—Clinical recovery made in three weeks, but Roentgen ray photograph shows slight degree of atelectasis present in the region of the fifth rib in the right mid-axillary line.

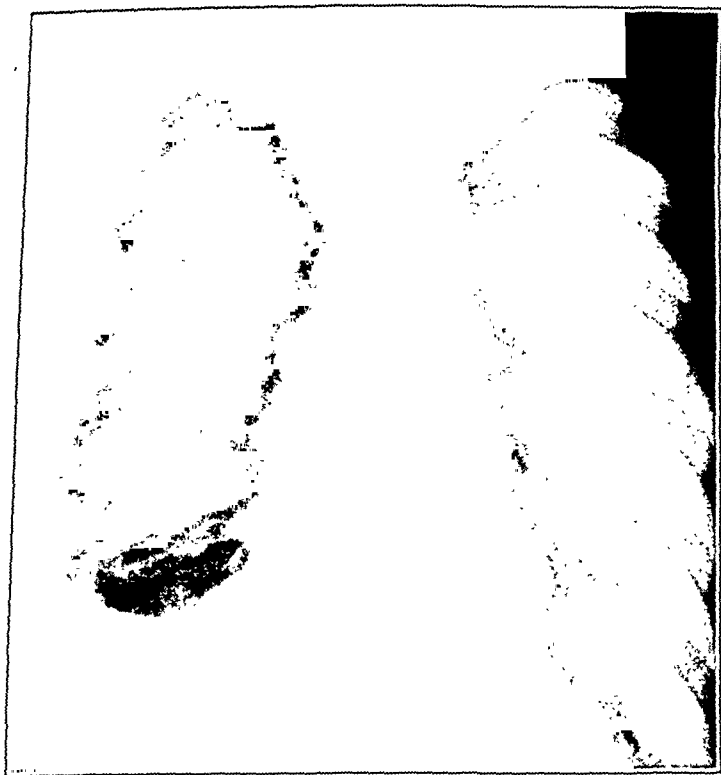


FIG. 3.—Roentgen ray photograph made eight weeks after collapse of right lung and three days prior to laparotomy. Lungs are normal. The heart and trachea are in normal position.

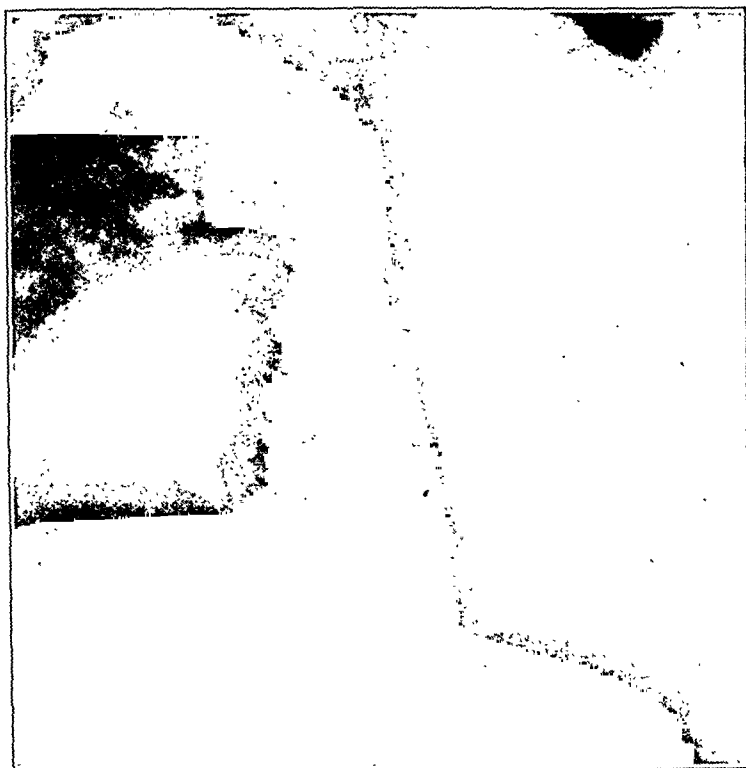


FIG. 4.—Roentgen ray photograph showing collapse of upper and middle lobe of right lung in case of lobar pneumonia. Although physical examination showed the right lung to be clearing the general condition grew worse due to failure of kidney function. The collapse of the lung occurred secondarily and thirteen days after the onset of pneumonia.

collapse is bilateral and persistent. These physical changes may furnish the soil for bronchopneumonia.

Case Reports. CASE I.—A man, aged fifty-one years, was admitted to the Jefferson Hospital March 14, 1926, suffering from epigastric pain after meals, nausea, vomiting and loss in weight. He had hematemesis ten years prior which was diagnosed, as due to ulcer of the duodenum. Since this attack he had been, on an ulcer diet, and free from symptoms. The past history otherwise discloses nothing worthy of note. His habits were very good. He did not suffer from respiratory infections. Generally his health was excellent until he suffered attacks of indigestion beginning in December, 1925, which gradually became worse and were accompanied by nausea and vomiting.

The physical examination on admission showed a well developed, symmetrical chest and expansion was equal. The percussion note over the lungs was resonant. No râles were present and the breath sounds were normal. The apex beat of the heart was visible in the fifth left interspace in the midclavicular line. The sounds occurred regularly and were well heard. No murmurs were present. The abdomen showed nothing worthy of note except slight epigastric tenderness.

Seven days after admission, on March 21, the patient, having vomited frequently, suddenly became cyanotic, developed cough and expectoration which was streaked with bright red blood and within six hours had a temperature of 101° F., a pulse of 92 and respirations of 30 per minute. Prior to this change he was not confined to bed. The right chest showed diminished expansion. There was dullness posteriorly over the apex of the right lung with bronchial breathing. A few coarse râles were noted. Anteriorly the percussion note was hyperresonant in the upper two-thirds of chest, breath sounds were distant and there were no râles. The lower third of right chest anteriorly and posteriorly gave a flat note. The apex of the heart was palpable in the fourth left interspace along the sternal border.

The leukocytes numbered 7800. Repeated examinations of the sputum were positive for blood and showed gram negative diplococci with a few pus cells. A diagnosis was made of collapse of the right lung. The patient continued to have a temperature ranging from 99° to 103° F. for a period of three weeks from onset. The pulse rate ranged from 70 to 122 per minute and the respirations from 20 to 48 per minute. The leukocyte count varied from 7800 to 17,200 and gradually returned to normal.

The Roentgen ray examination (Fig. 1) made March 29 showed a rather high degree of collapse of the right lung. The heart and trachea were displaced to the right. There was a small air-containing area in the right lower lobe, but the upper and middle lobes were entirely airless.

The patient made a clinical recovery in three weeks but the Roentgen ray (Fig. 2) examination at that time showed a slight degree of collapse present in the region of the fifth rib, mid-axillary line. The treatment was symptomatic, including codein in half-grain doses for cough.

The patient left the hospital and returned one month later for a surgical operation. Prior to operation a Roentgen ray examination (Fig. 3) showed the right lung to be normal. At operation the surgeon discovered an inoperable carcinoma of the stomach. The patient died six months later from the cancer of the stomach with metastasis to the liver. No further pulmonary symptoms developed.

The etiologic factors in the production of collapse were not evident. We believed that during the periods of vomiting he may have insufflated some of the vomitus which produced the obstruction and collapse.

During the violent paroxysms, he coughed up the insufflated material but the inflammatory reaction of the lung continued, gradually subsiding and the

lung returned to normal. There was no evidence of metastasis to account for lung symptoms.

The outstanding features during the collapse were the deep cyanosis which persisted for about one week, the blood spitting and the lack of any toxic symptoms, with a complete recovery from pulmonary symptoms with persisting gastric disturbances.

CASE II.—A man, aged fifty-five years, was admitted to the Jefferson Hospital April 4, 1927, with a history of having been ill for three days, beginning with a chill, fever, pain in right side, cough and blood spitting. The patient was mentally dulled, although able to be aroused sufficiently to answer questions. His past history was unimportant except that for twenty-five years he was a continuous user of whisky.

On physical examination, moderate cyanosis was present. Expansion was limited over the right chest. The percussion note was dull posteriorly over the right lung extending from the inferior angle of scapula to the liver. The breath sounds were distant and tubular in character. Occasionally râles were heard. The apex beat was palpated in the fifth left interspace midclavicular line. The sounds were well heard and there were no murmurs. The abdomen was tympanitic. The liver and spleen were not palpable.

The temperature was 101° F., the pulse rate 110 per minute and the respirations 32 per minute. The leukocyte count was 20,500. The urine showed a trace of albumin with many hyaline and granular casts.

The blood nonprotein nitrogen was 52.63 mg. per 100 cc. The sputum was positive for blood and pneumococci.

These findings suggested a lobar pneumonia involving the middle and lower lobes of the right lung.

On the second day in the hospital, the upper lobe of the right lung showed signs of consolidation, auricular fibrillation developed, and the patient's general condition was worse.

On April 10, six days after admission, his chest signs seemed to be clearing but his general condition did not seem to be greatly improved, due to his altered kidney function. A considerable quantity of tenacious sputum was being coughed up and caused the patient much distress.

On April 13, the physical signs of the patient changed: A tympanitic note was present over the right chest anteriorly over the upper and middle lobes. Below there was flatness. The signs on auscultation were also greatly altered. There was blowing breathing over the area of tympany. Over the flat area, neither râles nor breath sounds were heard. The heart was displaced toward the right.

Roentgen ray examination confirmed the physical findings and the clinical diagnosis of collapse of the right lung (Fig. 4).

The patient died on the fifteenth day of April from uremia. It was believed that the collapse was due to plugging of the bronchus with plugs of secretion.

Summary. 1. The occurrence of pulmonary atelectasis is reported in a case of pneumonia and in 1 of cancer of the stomach.

2. Pulmonary atelectasis occurs more frequently than is generally recognized in association with nonsurgical and nontraumatic cases.

3. It is a definite clinical entity, and readily diagnosed by its physical signs and clinical course.

4. Until more conclusive evidence is presented, the mechanical obstruction theory as to etiology is the most plausible since removal of the obstruction has resulted in prompt expansion of the lung.

Experimentally the condition has been reproduced in animals by the injection into their bronchi of material removed from the bronchi of patients suffering from pulmonary atelectasis. The abolition of the cough reflex in dogs followed by the introduction of an acacia solution into their bronchi has produced pulmonary atelectasis which disappeared when the acacia solution was aspirated through the bronchoscope.

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THE VOLUME AND HEMOGLOBIN CONTENT OF THE RED BLOOD CORPUSCLE.

SIMPLE METHOD OF CALCULATION, NORMAL FINDINGS, AND
VALUE OF SUCH CALCULATIONS IN THE ANEMIAS.

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THE work of Price-Jones^{1,2,3} has brought to the attention of the clinician the value of the determination of the size of red blood cells in the study of the blood. By the Price-Jones method, the diameter of the red cell is taken as a criterion of its size. It has been pointed out⁴ that the thickness of red cells is as variable as their diameter, or even more so, and that the determination of actual cell volume is therefore preferable to the measurement of

cell diameter. Determination of the actual amount of hemoglobin in each cell is of value in gaining a clearer conception than has been afforded by the determination of the various indexes regarding the nature of various types of anemia.

It is possible from a knowledge of the red-cell count, hemoglobin content, and total cell volume of a given sample of blood, to calculate the average volume of the individual red blood cells contained therein, as well as their hemoglobin content. It is obvious that where the total cell volume per unit of blood and the total number of cells per unit of blood, are known, the average volume of each cell can be calculated by a simple process of division. The volume of the average red blood corpuscle in a given sample of blood, expressed in cubic microns (or 10^{-12} cc.), is determined by dividing the cell volume, expressed in cc. per 1000 cc. of blood, by the red-cell count, expressed in millions (and fraction thereof) per cubic millimeter of blood. To avoid confusion with total cell volume, it is suggested that the term "corpuscular volume" be used when referring to the volume of the individual red blood corpuscle. It is used hereafter with this meaning.

Similarly, where the amount of hemoglobin per unit of blood and the number of corpuscles per unit of blood, are known, the determination of the amount of hemoglobin in each corpuscle is easily made. This is concerned with the same properties as the well known "color index," but is differently expressed. The hemoglobin content, expressed in grams per 1000 cc., divided by the red-cell count, expressed in millions per cubic millimeter, gives the hemoglobin content of the average red cell in 10^{-12} gm. This will be referred to, hereafter, as "corpuscular hemoglobin."

The actual proportion of the substance of each red cell taken up by hemoglobin may be calculated by dividing the corpuscular hemoglobin by the corpuscular volume; or, directly, by dividing the hemoglobin content of a given sample of blood, expressed in grams per 100 cc., by the total cell volume expressed in cc. per 100 cc.

Illustration of Method of Calculation. A sample of blood is found to contain 5.85 million red cells per c.mm., 15.87 gm. of hemoglobin per 100 cc. (or 158.7 gm. per 1000 cc.), and 46.5 cc. of packed red cells per 100 cc. of blood (or 465 cc. per 1000 cc.). Then, the average

corpuscular volume is $\frac{465}{5.85} = 79.5$ c. μ . (or 79.5×10^{-12} cc.);

the average corpuscular hemoglobin is $\frac{158.7}{5.85} = 27.1 \times 10^{-12}$ gm.;

proportion of hemoglobin in the average cell is $\frac{27.1}{79.5} \times 100 = 34.1$

per cent (or $\frac{15.87}{46.5} \times 100 = 34.1$ per cent).

For calculations such as have been described to be of any value, it is of course first essential that accurate methods be used in deter-

mining cell count, hemoglobin content and cell volume. The accurate determination of hemoglobin content is a difficult problem. For the research worker the very accurate method of determining the oxygen capacity of blood (van Slyke⁵) is available, but the various clinical hemoglobinometers have been shown to be inaccurate.^{6,7} The writer⁸ has found that the Newcomer instrument, although inaccurate as obtained from the manufacturer, is consistent in its error when compared with readings by the van Slyke apparatus, so that a correction curve can be plotted. Readings by the Sahli instrument are higher than those determined by the van Slyke method. The error, although not as consistent in degree as is that of the Newcomer instrument, is sufficiently regular to render the instrument of some value when a correction is made.

Accurate determinations of cell volume can be made by centrifuging a quantity of blood in a carefully calibrated tube. It is important, however, that due allowance be made for any change in the normal osmotic pressure of the blood and consequent effect on total cell volume resulting from the method used in collecting the blood. Thus it has been found⁸ that the addition of 20 mg. of solid neutral potassium oxalate to 10 cc. of blood results in a decrease of cell volume of 3.68 per cent, while the addition of 40 mg. to 10 cc. of blood causes a shrinkage of 6.7 per cent.

The Volume of the Normal Red Blood Corpuscle. Starling,⁹ as the result of the measurement of models of high magnification, gives the volume of the normal red blood cell as being 0.0000000722 c.mm. (or 72.2 c. μ). Wintrobe and Miller⁸ report elsewhere cell counts, hemoglobin and cell volume determinations in 100 healthy young men residing in the South. In Table I are found the calculated corpuscular volume and hemoglobin of each of these bloods. The average corpuscular volume was 79.8 c. μ . Fig. 1 shows that 80 per cent ranged between 70 and 87 c. μ .

TABLE I.—ABSOLUTE CELL DETERMINATIONS IN ONE HUNDRED NORMAL YOUNG MEN.

Subject.	Age.	Red cell count, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Corpuscular volume, c. μ .	Corpuscular hemoglobin, 10 ⁻¹² gm.	Proportion of hemoglobin in cell.
1	19	5.48	13.40	83.8	24.5	29.2
2	24	5.69	14.50	59.9	25.5	42.5
3	22	5.59	15.25	74.1	27.3	36.8
4	24	6.61	16.20	75.2	24.5	32.5
5	21	6.09	16.05	82.3	26.4	32.0
6	22	5.54	16.60	86.5	29.9	34.6
7	23	6.03	16.20	79.0	26.9	34.1
8	27	5.20	16.20	90.2	31.2	34.7
9	27	4.68	15.93	85.9	34.0	39.6
10	28	5.88	16.05	78.0	27.3	35.0
11	23	5.40	16.75	89.5	31.0	34.7
12	22	5.53	18.30	84.3	32.9	39.1
13	22	5.32	16.75	96.8	31.5	32.4
14	24	4.70	16.33	78.3	34.7	44.3

TABLE I.—ABSOLUTE CELL DETERMINATIONS IN ONE HUNDRED
NORMAL YOUNG MEN.—*Continued.*

Subject.	Age.	Red cell count, millions per c.mm.	Hemoglo- bin, gm. per 100 cc.	Corpuscu- lar volume, c.c.	Corpuscu- lar hemo- globin, 10 ⁻¹² gm.	Proportion of hemo- globin in cell.
15	22	5.84	17.02	68.9	29.1	42.2
16	24	5.32	16.90	85.2	31.8	37.3
17	21	5.37	16.05	72.5	29.9	41.3
18	20	5.58	17.25	78.0	30.9	39.6
19	25	6.53	17.25	73.7	26.4	35.8
20	25	5.14	15.65	84.3	30.4	36.1
21	23	5.64	14.80	85.0	26.1	30.7
22	21	5.62	16.00	81.8	28.5	34.8
23	22	5.99	15.95	63.3	26.6	42.0
24	25	6.15	16.60	76.8	27.0	35.0
25	21	6.67	16.35	64.7	24.5	37.9
26	21	5.46	16.25	90.0	29.8	33.2
27	23	5.27	15.80	93.0	30.0	32.2
28	23	4.98	16.05	94.5	32.2	33.8
29	23	5.18	15.24	97.5	29.4	30.2
30	21	6.69	16.20	70.0	24.2	34.6
31	21	5.58	16.05	83.0	28.8	34.7
32	24	6.71	17.50	84.3	26.1	31.0
33	26	5.80	15.23	78.5	26.3	33.5
34	24	5.71	15.38	79.6	26.9	33.8
35	25	5.24	15.77	78.4	30.1	38.4
36	28	5.45	16.66	89.6	30.6	34.2
37	24	5.57	16.95	82.7	30.4	36.8
38	24	5.75	16.27	75.0	28.3	37.7
39	24	5.52	15.25	85.8	27.6	32.2
40	25	6.12	16.48	77.3	26.9	34.8
41	22	5.86	16.25	80.8	27.7	34.2
42	24	6.21	15.93	70.2	25.7	36.7
43	21	5.30	15.45	88.1	29.2	33.2
44	22	5.97	15.48	81.4	25.9	31.8
45	23	5.55	16.00	81.0	28.8	35.6
46	22	6.33	15.93	81.4	25.2	31.0
47	23	6.23	16.75	78.2	26.9	34.4
48	25	6.41	16.00	77.7	26.1	33.6
49	23	5.94	16.40	80.0	27.6	34.7
50	23	5.74	15.94	68.9	27.8	40.4
51	23	7.35	17.85	74.0	24.3	33.0
52	23	6.57	16.70	73.7	25.4	34.7
53	21	6.19	16.55	84.4	26.7	31.7
54	23	7.53	15.70	62.7	20.9	33.6
55	25	6.64	16.00	73.5	24.1	33.0
56	25	6.88	17.35	71.7	25.2	35.2
57	25	6.61	16.10	79.9	24.4	30.6
58	24	6.35	16.10	79.6	25.4	31.9
59	23	6.36	15.80	71.4	24.8	34.8
60	24	6.46	17.60	80.3	27.2	34.1
61	25	5.09	14.50	81.6	28.5	34.9
62	27	6.29	17.50	70.5	27.8	39.4
63	26	6.24	14.80	73.0	23.7	32.5
64	23	4.82	14.30	83.6	29.7	35.5
65	22	5.35	15.60	83.8	29.2	34.8
66	23	5.87	15.22	71.8	25.9	36.0
67	30	6.24	16.60	82.4	26.6	32.2
68	25	5.58	15.50	86.5	27.8	32.2
69	21	4.94	15.40	95.0	31.2	32.8
70	22	6.18	16.05	81.6	26.0	31.8
71	22	6.34	16.05	82.9	25.3	30.6
72	22	6.13	15.50	68.5	25.3	37.0

TABLE I.—ABSOLUTE CELL DETERMINATIONS IN ONE HUNDRED NORMAL YOUNG MEN.—*Continued.*

Subject.	Age.	Red cell count, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Corpuscular volume, c.μ.	Corpuscular hemoglobin, 12 ⁻¹² gm.	Proportion of hemoglobin in cell.
73	21	5.55	15.65	86.4	28.2	32.7
74	21	5.44	15.85	84.5	29.1	34.4
75	21	5.86	16.20	83.3	27.6	33.1
76	28	5.67	14.30	74.1	25.3	34.1
77	27	5.86	13.70	80.6	23.4	29.0
78	24	5.38	13.75	85.1	25.6	30.1
79	24	6.21	14.30	74.1	23.0	31.0
80	21	5.78	14.35	81.8	24.8	30.3
81	21	6.31	15.65	81.1	24.8	30.6
82	25	5.89	16.20	82.1	27.5	33.5
83	24	6.11	16.20	80.8	26.5	32.8
84	23	6.89	16.42	71.5	23.8	33.3
85	30	5.96	16.28	81.7	27.3	33.4
86	24	6.00	16.38	83.7	27.3	32.6
87	22	6.79	16.75	74.0	24.7	33.4
88	28	5.17	14.20	80.2	27.5	34.3
89	25	5.57	15.85	82.4	28.5	34.5
90	30	5.39	16.42	93.4	30.5	32.7
91	21	5.90	15.18	69.6	25.7	36.9
92	23	6.60	17.00	77.3	25.8	33.3
93	27	5.78	15.80	84.1	27.2	32.3
94	24	5.13	14.30	83.0	27.9	32.4
95	25	5.61	15.30	76.5	27.3	35.7
96	29	6.44	15.24	71.7	23.7	33.1
97	26	5.34	14.65	76.6	27.4	35.8
98	29	5.68	14.45	75.6	25.4	33.6
99	21	5.61	14.36	83.4	25.6	30.7
100	28	5.01	14.30	88.5	28.5	32.2
Average		5.85	15.87	79.8	27.3	34.4

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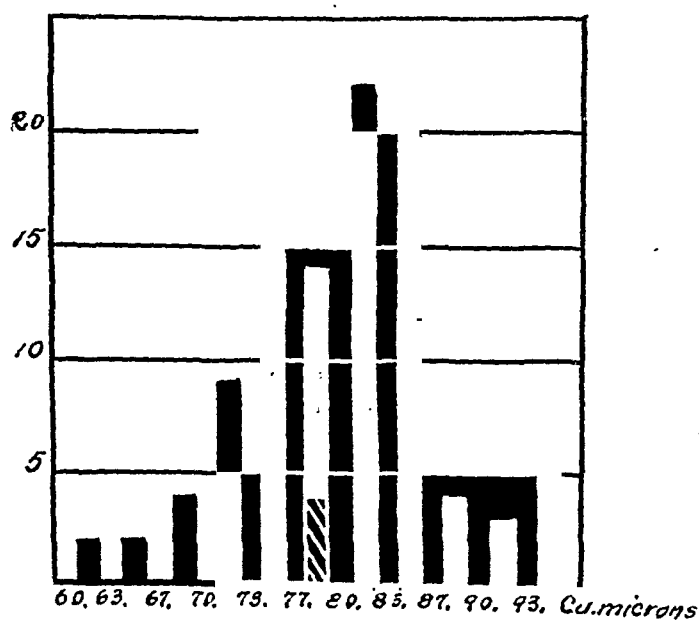


FIG. 1.—Volume of average red blood cell in one hundred healthy young men.

In Table II are found the average, maximum and minimum corpuscular volumes as calculated from the available reliable data for normal young men between nineteen and thirty years of age.

TABLE II.—VOLUME OF RED BLOOD CORPUSCLES IN HEALTHY YOUNG MEN (EXPRESSED IN C. μ .).

Author.	No. of men.	Average.	Maximum.	Minimum.
Osgood ⁷ (Oregon)	94	86.1	95.5	71.3
Haden ¹⁰ (Kansas City)	20	91.9	97.0	87.0
Gram and Norgaard ¹¹ (Denmark)	7	85.2	88.7	82.9
Bie and Möller ¹² (Denmark)	10	83.9	90.0	76.7
Wintrobe and Miller ³ (Louisiana)	100	79.8	97.5	59.9
Averages		83.8	95.6	68.3

The average corpuscular volume in the South appears to be definitely lower than that calculated for other parts of the world. This may be due to a difference in technique or be the effect of climate. The very high and the very low figures recorded are probably the result of technical error. Our lowest figure (59.9) was partially due to the occurrence of some hemolysis in the centrifugated specimen.

The average corpuscular volume as calculated from reliable data for the blood of healthy young women between eighteen and thirty years of age, is as follows:

TABLE III.—AVERAGE CORPUSCULAR VOLUME IN HEALTHY YOUNG WOMEN.

Author.	No. of women.	Average volume, C. μ .
Osgood ¹³	100	88.5
Haden ¹⁰	9	92.8
Gram and Norgaard ¹¹	6	88.0
Bie and Möller ¹²	10	81.7
Total	125	88.2

The average figure for young women is somewhat higher than that for men of the same age, probably largely on account of the fact that figures for women in the South are not available. In 115 of the above cases, the corpuscular volume ranged from 98.1 to 76.5 c. μ .

Accurate statistics for the calculation of normal corpuscular volume in other age groups are not available.

Attempts made to ascertain the possibility of the identification of different races of mankind through the application of micrometry¹⁴ failed because of the normal variation in the size of cells. Price-Jones¹⁵ considers that there is a diurnal variation in size. The variation in corpuscular volume indicated by the figures enumerated above, aside from the extremes resulting from technical error, is, therefore, probably a true manifestation of the normal.

As between the two sexes, there appears to be only a slight difference in size, the cells of females being slightly larger. The normal range in size of red cells for young adults of both sexes may, therefore, probably be taken as being between 70 and 98 c. μ . with the great majority occurring well within these figures.

It is interesting to compare these normal figures with findings in various conditions of anemia. Haden¹⁰ found an average corpuscular volume of 128 c. μ in 20 cases of pernicious anemia. The lowest figure was 108 c. μ (a case in the stage of remission), while the highest was 163 c. μ . Again, in 26 cases of hemolytic secondary anemia of various types, the corpuscular volume ranged from 63 to 97 c. μ . In 8 cases of hemorrhagic secondary anemia the cells ranged from 62 to 74 c. μ in size with an average of 71 c. μ .

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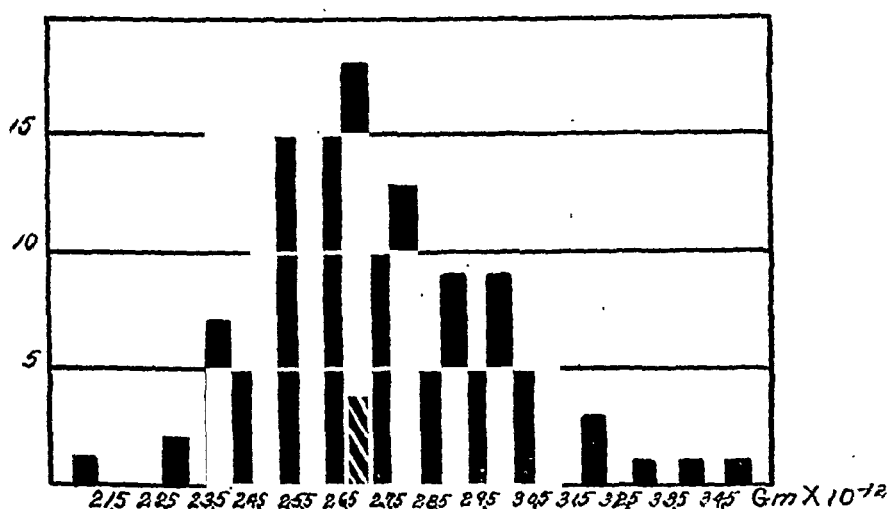


FIG. 2.—Grams of hemoglobin in average cell in one hundred healthy young men.

Haden points out that a relatively small increase in the diameter causes a relatively great increase in its volume. An increase in diameter of 1 μ causes an increase in cell volume of approximately 44 per cent. It seems to me that much of the valuable information obtained by measuring the diameter of red cells in pernicious anemia can be more easily gained by the simple calculations described above. There is the theoretical objection that where there are many microcytes as well as macrocytes (that is, the Price-Jones curve has a broad base) the increase in corpuscular volume may be obscured by the calculation of an *average* corpuscular volume. Practically, however, there are usually enough macrocytes present to produce a noticeable increase in the average corpuscular volume; that is, the Price-Jones curve is definitely swung to the right. In pernicious anemia, just as the volume index is always above 1, so the corpuscular volume is always greater than normal.

Hemoglobin Content of the Normal Red Blood Corpuscle. In Table IV are found average, maximum and minimum corpuscular hemo-

TABLE IV.—HEMOGLOBIN CONTENT OF RED CELLS IN HEALTHY YOUNG MEN (EXPRESSED IN 10^{-12} GM.).

Author.	No. of men.	Average.	Maximum.	Minimum.
Osgood ⁷ (Oregon)	137	29.2	35.7	24.6
Haden ¹⁰ (Kansas City)	20	31.1	33.4	29.2
Gram and Norgaard ¹¹ (Denmark)	7	27.6	28.2	27.3
Bie and Möller ¹² (Denmark) . .	10	26.7	28.8	25.4
Wintrobe and Miller ³ (Louisiana)	100	27.3	34.7	23.0
Averages	28.7	34.7	24.5

globin as calculated from the data supplied by various authors for normal young men between the ages of nineteen and thirty years. Frequency Fig. 2 shows that 91 per cent of the men examined by Wintrobe and Miller had cells containing an average of 23.5 to 31.5 $\times 10^{-12}$ gm. of hemoglobin.

For normal young women between eighteen and thirty years of age, calculated corpuscular hemoglobin is as follows:

Osgood,¹³ 100 women, averaging 28.5×10^{-12} gm.

Haden,¹⁰ 9 women, averaging 31.3×10^{-12} gm.

Gram and Norgaard,¹¹ 6 women, averaging 27.9×10^{-12} gm.

Bie and Möller,¹² 10 women, averaging 28.1×10^{-12} gm.

Total, 125 women, averaging 28.6×10^{-12} gm.

In 115 of these individuals, the highest corpuscular hemoglobin was 33.8×10^{-12} gm., while the lowest figure was 23.7×10^{-12} gm.

From these calculations it appears, therefore, that the red blood corpuscles of the blood of healthy young adults contain an average of 28.7×10^{-12} gm. of hemoglobin and that the normal range occurs between approximately 24 and 33×10^{-12} gm.

In Table V, the actual proportion of hemoglobin contained in normal red blood cells, as calculated from the data of the various

TABLE V.—PROPORTION OF HEMOGLOBIN IN NORMAL RED BLOOD CELLS.

Author.	No. of men.	Average.	Maximum.	Minimum.
Osgood ⁷ (Oregon)	94	33.1	43.8	30.4
Haden ¹⁰ (Kansas City)	20	33.9	36.2	32.2
Gram and Norgaard ¹¹ (Denmark)	7	32.4	33.7	30.8
Bie and Möller ¹² (Denmark) . .	10	31.8	33.1	29.4
Wintrobe and Miller ³ (Louisiana)	100	24.4	44.3	29.0
Averages	33.7	42.6	29.9

authors quoted, is indicated. Fig. 3 shows that in 84 per cent of the men examined by Wintrobe and Miller hemoglobin content of the average cell ranged from 30 to 37 per cent.

The corresponding figures for women of the same age are:

Osgood,¹³ 100 women, averaging 32.2 per cent.

Haden,¹⁰ 9 women, averaging 33.7 per cent.

Gram and Norgaard,¹¹ 6 women, averaging 31.7 per cent.

Bie and Möller,¹² 10 women, averaging 34.4 per cent.

Total, 125 women, averaging 32.5 per cent.

The highest proportion of hemoglobin in 115 of these women was 37.2 per cent, while the lowest figure was 28.1 per cent.

The average for the two sexes is 33.3 per cent. A slightly lower percentage of hemoglobin appears to be present in the cells of women than in those of men of the same age. The great majority of the figures range between 30 and 40 per cent. This is in fair agreement with the stated composition of healthy red blood cells, namely: water, 56.5 parts; absolute hemoglobin, 41.1 parts; other proteids, fats, and so forth, 2 to 4 parts.¹⁶

CASES



Fig. 3.—Percentage of hemoglobin in average red cell in one hundred healthy young men.

Determination of the absolute hemoglobin content of cells is of particular interest in the consideration of pernicious anemia. In this disease, the characteristic change is an increase in the volume of the red blood cells. These cells, however, are not supersaturated with hemoglobin, as is commonly supposed. They frequently do contain more hemoglobin than is found in normal cells, but this increase is never as great as the increase in the volume of the cell. Thus Haden¹⁰ found in 20 cases of pernicious anemia that the cells contained from 21.1 to 46.8 $\times 10^{-12}$ gm. of hemoglobin with an average of 37.5 $\times 10^{-12}$ gm. The actual percentage of hemoglobin in these cells, however, ranged from 16 per cent to 34.9 per cent and in not 1 case did it exceed the normal limit. Likewise, the saturation index never rose above 1.

The Relation between Absolute Cell Determinations and the Indexes.

The relationship between absolute cell determinations and the three indexes is probably best illustrated graphically:

$$\frac{\text{Vol. (cc. per 1000 cc.)}}{\text{R.B.C. (in millions)}} = \frac{\text{corpuscular volume in c.}\mu}{\text{R.B.C., per cent}} = \frac{\text{Vol., per cent}}{\text{R.B.C., per cent}} = \text{volume index.}$$

$$\frac{\text{Hb. (gm. per 1000 cc.)}}{\text{R.B.C. (in millions)}} = \frac{\text{corpuscular hemoglobin in } 10^{-12} \text{ gm.}}{\text{R.B.C., per cent}} = \frac{\text{Hb., per cent}}{\text{R.B.C., per cent}} = \text{color index.}$$

$$\frac{\text{Hb. (gm. per 100 cc.)}}{\text{Vol. (cc. per 100 cc.)}} = \frac{\text{proportion of hb. in cell;}}{\text{Vol., per cent.}} = \frac{\text{Hb., per cent}}{\text{Vol., per cent.}} = \text{saturation index.}$$

From the above, it can be seen that corpuscular volume and volume index express the same relationship with the difference that the latter is an expression of the volume of the average cell in proportion to the normal volume and red-cell count. Similarly, both corpuscular hemoglobin and color index refer to the actual amount of hemoglobin in the average cell, with the difference that color index expresses that amount *in proportion to the normal*—a “normal” which, by the way, has, heretofore at least, been based on inaccurate and unreliable data. The last formula shown above expresses the actual proportion of the substance of each cell taken up by hemoglobin, the saturation index expressing this proportion in terms of normal.

These simple methods of making absolute cell determinations are not offered to replace the indexes. It is believed, however, that such calculations do afford a clearer conception of the details of size and hemoglobin content of red cells, as well as a better understanding of the meaning of the indexes. Furthermore, the accurate determination of the indexes presupposes a knowledge of the true normal. As long as our generally accepted figures for normal—particularly normal hemoglobin content of blood—are as varied and inaccurate as they now are, absolute cell determinations have a particular value.

Summary. 1. Simple methods for the calculation of the volume of the individual red blood corpuscle, as well as its hemoglobin content, are described.

2. The terms, “corpuscular volume,” and “corpuscular hemoglobin” are defined, and the normal corpuscular volume and corpuscular hemoglobin, as calculated from accurate data supplied by various authors, are given.

3. The value of absolute cell determinations in the anemias is briefly discussed and their relationship to the indexes indicated.

Conclusions. The red blood corpuscles of the blood of healthy young adults vary between 70 and 98 c. μ in size, with the majority well within these figures. The average cell contains 28.7×10^{-12} gm. of hemoglobin, the latter constituent taking up, on the average, 33.3 per cent of the entire substance of the cell.

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BLOOD SEDIMENTATION TEST COMBINED WITH A SERUM REACTION IN THE DIAGNOSIS AND PROGNOSIS OF TUBERCULOSIS.

A PRELIMINARY STUDY OF ONE HUNDRED AND FORTY-SEVEN CASES.

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VARIATIONS in the rate of sedimentation of blood cells in healthy and diseased individuals, phenomena noted by ancient observers, have given rise to a considerable amount of recent experimentation. The work of Fahreus in 1918 and, more recently, of Westergreen

and others has served to put the test on a stronger foundation, and it can now be definitely stated that a distinct and more or less constant correlation has been established between erythrocyte suspension stability and quantitative tissue destruction processes in the human body. The reaction is, however, nonspecific and gives parallel results in pelvic inflammatory disease, acute infections, tuberculosis, and so forth. It is only when the disease condition is definitely identified or when all but one of the conditions known to produce the sedimentation phenomena are ruled out that it can be used as an accurate measure of pathologic activity attributable to that disease. It has seemed to be of considerable value as an aid in determining the *status præsens* and estimating the prognosis in tuberculosis, but, here again, one of its chief limitations has been its nonspecificity.

It is to attempt to overcome this factor that, in conducting the investigation detailed in this report, the blood sedimentation test has been performed in conjunction with a serum test which has for its object the determination of the presence or absence of active tuberculosis. The serum test employed here is one which depends for its positive result upon precipitin phenomena occurring in the presence of tuberculous precipitin and possibly other specific antibodies in the patient's serum. The reaction is, therefore, intended merely as a means for ascertaining the presence and approximate combining power of tuberculous antibodies in the blood serum of a given patient. It involves the use of a water-soluble extract of tubercle bacilli prepared by Eli Lilly & Co., and marketed under the trade name "Tubercumet." The suspension stability test which has been used here is essentially that employed by Jacob Cutler and described as his "finger-puncture method;" however, we have used blood obtained by venipuncture, another portion of the same specimen being used for the serum reaction. A brief description of the technique follows:

Technique. Under aseptic conditions, about 5 cc. of blood is obtained by puncture of an arm vein. It is best to secure this blood at least two hours after the patient's last meal, in order to have it as free from fats as possible; these are said to interfere with the precipitin reaction: 1.8 cc. of the blood is placed in a test tube containing 0.2 cc. of a 3 per cent solution of sodium citrate, and thoroughly mixed; this prevents clotting in the specimen used for the sedimentation test. The remainder of the whole blood is allowed to clot, the clot and cells separated by centrifugalization and the clear serum drawn off; this serum is refrigerated for twenty-four hours before use in the precipitin test.

Sedimentation Test. The citrated blood, thoroughly shaken and mixed to assure absence of clotting and good suspension of cells, is drawn up in a special pipette calibrated in cubic millimeters, to form a solid column of 40 c.mm. This pipette is the type used by

Cutler in his finger-puncture method. The time is noted, and readings of the height of the column of sedimenting cells are taken at five-minute intervals for one hour; these readings are recorded and embodied in a graph, the abscissæ of which represent the height of the cell column and the verticals of which are the five-minute time intervals. The curve so obtained is a graphic representation of the amount, rate and changes of rate of sedimentation, and may be classified in one of four arbitrarily constructed types:

1. Horizontal Line (Hor. L.), in which sedimentation is not complete within one hour, and amount of sedimentation is within normal limits. In adopting standards of normal limits, use has been made of the results reported by Greisheimer and by Cutler, and of the 16 normal cases of our group. The limit of amount of sedimentation is here considered as 9 mm. per first hour for males, 11 mm. for females.

2. Diagonal Line (Diag. L.), in which sedimentation is not complete within one hour, but amount is beyond normal limits.

3. Diagonal Curve (Diag. C.), in which sedimentation is complete within one hour, and the amount is less than 20 mm. at the end of the first fifteen minutes.

4. Vertical Curve (Vert. C.), in which sedimentation is complete within one hour and the amount is 20 mm. or more at the end of the first fifteen minutes.

Serum Test. One-fifth cubic centimeter of clear serum which has been refrigerated twenty-four hours is carefully overlaid in a small test tube (5 mm. diameter) with an equal amount of the water-soluble extract of tubercle bacilli, "Tubercumet." The entire test is performed under sterile conditions. The tube is examined for a ring at the interface of the two substances immediately and again at half-hour intervals for two hours, during which time it is kept in an incubator at 37° C. Following this, the tube is allowed to stand at room temperature for twenty-four hours and a sixth reading taken. The presence of a hazy, indefinitely margined ring of almost immediate formation may be disregarded, as it is probably due to a fat reaction; such a ring is further identified by its remaining unchanged at the interface through the twenty-four-hour period. The true "Tubercumet" ring is a clearly defined one which forms more slowly, may continue to broaden during the two hours of incubation and either disappears after twenty-four hours or has moved to the upper surface of the extract, from which it clouds downward on gentle agitation. The width and definition of the ring are said to be proportional to the quantity of precipitin antibody in the patient's serum. The ring varies from 0.5 to 5 mm. in diameter and may be classified as:

Slight (SR) 0 to 1 mm.

Moderate (MR) 1 to 3 mm.

Heavy (HR) 3 to 5 mm.

Interpretation of Findings. In a general way, most observers agree that the amount and rapidity of sedimentation are proportionate or, at least, parallel to the amount and rapidity of pathologic activity and tissue destruction. The curve obtained here represents this amount and rapidity graphically. If we assume it to be a fair measure of pathologic activity, the sharper the declivity of the curve, the greater the amount and speed of tissue destructive processes in the individual from whom the blood was obtained. The "Tubercumet" test, essentially a ring reaction, depends for its positive result upon the presence of tuberculous precipitin in the patient's serum. This antibody, it is then to be expected, should be found in:

1. The blood of tuberculous patients in some degree of direct proportion to their resistance to the pathologic process.

2. Some patients with healed lesions where antibodies are still present in the tissues. Negative precipitin reaction, conversely, should indicate the absence of antibody substances, and might be found in:

- (a) The absence of tuberculous infection.
- (b) Early cases in which antibodies have not yet developed.
- (c) Far-advanced cases in which almost all resistance is broken and the body has almost ceased to produce precipitins.
- (d) Old lesions where the need for their continued production has ceased.

Each of the tests may terminate, depending upon extent and rapidity of reaction, in one of four arbitrarily constructed types. They give us, theoretically at least, a means of estimating, in one case, something of the general tissue destruction occurring in the body and, in the other, something of the presence and strength of the individual's specific reaction to tuberculosis. It is evident that where the two tests are performed upon the same individual (here, upon portions of the same specimen of blood), there are sixteen possible combinations of the types of end result: Horizontal line sedimentation with negative serum reaction, diagonal line sedimentation with negative serum reaction, and so forth. If we assume each of the tests to be performing, with some efficiency and reliability its particular function, the following interpretation of results is logically suggested in Table I.

Analysis of Cases. A total of 147 individuals was used for this series of tests, divided into groups as follows: Normals, observation cases, incipient cases, moderately advanced and far-advanced cases. The latter two groups were further divided into A, B and C types.

I. Normal Individuals. Of our normal group, 7 were male and 9 female. All of these 16 showed negative precipitin reactions. The sedimentation of our males varied 1.5 to 9 mm., only 1 going below 5 during the hour. Among the females the sedimentations

varied from 1.5 to 10.5 mm., these results being a little higher than those obtained by most observers.

TABLE I.—SEDIMENTATION TESTS AND TUBERCUMET REACTION.

SEDIMENTATION.

	Horizontal L.	Diagonal L.	Diagonal C.	Vertical C.
Tubercu- met NEG.	1. No tuberculosis 2. Arrested tubercu- losis; antibod- ies disappeared	1. No tuberculosis; some slight destruc- tive disease 2. Apparently ar- rested tubercu- losis	1. No tuberculosis; some destruc- tive disease	1. No tuberculosis; some destructive disease. 2. Last stages of tuberculosis; a rapid decline and practically no re- sistance.
SR.	1. Incipient tuber- culosis 2. Apparently ar- rested tubercu- losis	1. Incipient tuber- culosis 2. Improving tuber- culosis 3. Very slowly pro- gressive tuber- culosis*	1. Tuberculosis plus some destruc- tive disease 2. Tuberculosis; a poor resistance	1. Tuberculosis plus some destruc- tive disease. 2. Tuberculosis; a rapid decline and practically no resistance.
MR.	1. Incipient tuber- culosis 2. Improving tuber- culosis 3. Apparently ar- rested tubercu- losis	1. Incipient tuber- culosis 2. Improving tuber- culosis 3. Slowly progres- sive tuberculo- sis*	1. Tuberculosis plus some destruc- tive disease 2. Tuberculosis; a fair resistance	1. Tuberculosis plus some destruc- tive disease. 2. Tuberculosis; a poor resistance.
HR.	1. Incipient tuber- culosis 2. Improving tuber- culosis 3. Almost arrested tuberculosis	1. Improving tuber- culosis 2. Tuberculosis; good resistance	1. Tuberculosis plus some destruc- tive disease 2. Tuberculosis; fair resistance	1. Tuberculosis plus some destruc- tive disease. 2. Extensive tuber- culosis; a strong body reaction.

* For example, fibroid.

TABLE II.—OBSERVATION CASES.

Name.	Sex.	Race.	Age.	Spu- tum.	Wt.	Temp.	Complications.	Tuber- cumat.	Sedimentation.	
									Curve.	Amt., mm.
V. A.	M.	W	38	Neg.	Const.	Const.	Pneumonokoniosis	Neg.	Hor. L.	2.5
E. D.	F.	W	27	Neg.	Incr.	Sl.	SR.	Not done	
M. O'R.	M.	W	45	Neg.	Const.	Norm.	Pneumonokoniosis	SR.	Diag. L.	14.0
A. L.	M.	W	39	Neg.	Incr.	Sl.	Empyema	SR.	Diag. C.	28.5
M. Z.	F.	W	20	Neg.	Const.	Sl.	Chronic nephritis, cold abscess, is- chio rectal ab- scess, bone dis- ease	SR.	Vert. C.	32.0

II. *Observation Cases.* The observation cases number 5, all of which have negative sputa and have never shown pulmonary involvement on physical examination. However, in only 1 of these was the Tubercumat test negative, and in this same one the sedimentation was within normal limits. The remaining 4 gave slight positive precipitin reactions and sedimentations varying from diagonal line to vertical curve. It is to be noted that each of these presented some complication of a more or less destructive nature, the least sedimentation occurring in a case with pneumo-

nokoniosis and emphysema, the next in a patient with pleural empyema, and the highest in a case complicated by various foci of destructive lesions. Actual pulmonary involvement may not have been sufficient for determination by physical diagnosis.

III. Incipient Cases. In this group of 9 patients it is notable that, while all offered sufficient history or symptomatology to be placed in a sanatorium as incipient cases of pulmonary tuberculosis, in 2 cases the precipitin tests were negative. Further investigation, however, shows that one of these has also a normal sedimentation and that there has always been grave doubt as to the diagnosis of tuberculosis; the other presents a diagonal line type of sedimentation curve and has by clinical signs only a healed lesion. The single case presenting a slight precipitin reaction occurred in an apparently very early case clinically. It is interesting to note that, of the three moderate precipitin reactions, the highest sedimentation, a diagonal curve, occurred in the one case which had had hemoptysis. The three heavy precipitin reactions, all showing horizontal line (normal) or diagonal line curves, would seem to indicate a high degree of antibody formation coupled with quite low-grade tissue destruction; in other words, a high resistance on the part of the patient's tissues.

IV. Moderately Advanced "A" Cases. The 8 negative Tubercumet reactions of this group occurred in a wide variety of cases. Of the 3 presenting normal sedimentation curves, 2 were apparently arrested cases, while the third was one in which the true condition was probably a cardiac one; the 3 cases with diagonal line sedimentation curves included 1 arrested, 1 healed and 1 of questionable tuberculosis with absence of pulmonary signs; the remaining 2 negative reactions were obtained in 2 rapidly declining patients who could no longer be included in the moderately advanced "A" cases.

Of the 7 slight positive reactions, 2 cases showed normal sedimentation charts; the 2 highest sedimentations, 1 diagonal line and 1 diagonal curve, occurred in the 2 patients who had had previous hemoptysis.

The three moderate reactions all occurred in patients presenting positive sputa and moderately high grades of sedimentation, all diagonal curves of 22 to 24 mm.

The six heavy Tubercumet reactions were all in patients having positive sputa and, with the exception of a single diagonal line of 18.5 mm., diagonal curve sedimentations; the 3 highest grades of sedimentation occurred in the three members of the group who were consistently showing loss of weight.

V. Moderately Advanced "B" Cases. Two of the three negative Tubercumet reactions in this group illustrate the conception that such a result is obtainable in a lesion where healing has occurred with resultant fibrosis and subsequent disappearance of the anti-

TABLE III.—INCIPIENT CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercu- met.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
O. P.	F.	W	34	...	Gain	Norm.	Old pleurisy	Neg.	Hor. L.	6.0	Doubtful tuberculosis. Healed lesion.
J. C.	F.	W	18	...	Gain	Norm.	Neg.	Diag. L.	15.0	
E. P.	F.	W	39	...	Gain	Norm.	Chronic bronchitis	Sl. pos.	Not done	done	
L. F.	M.	W	23	+5	Gain	Norm.	Mod. pos.	Diag. L.	11.0	
A. F.	F.	W	39	...	Gain	Norm.	Mod. pos.	Diag. L.	24.0	
J. D. M.	F.	W	21	...	Gain	Norm.	Hemoptysis	Mod. pos.	Diag. C.	26.5	
A. A.	M.	B	46	...	Gain	Sl.	Heavy pos.	Hor. L.	4.5	
E. R.	M.	W	18	...	Gain	Norm.	Heavy pos.	Hor. L.	9.0	
F. A.	F.	W	24	...	Gain	Norm.	Heavy pos.	Diag. L.	23.0	

TABLE IV.—MODERATELY ADVANCED "A" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercu- met.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
G. F.	M.	W	21	...	Gain	Norm.	Hemoptysis	Neg.	Hor. L.	1.0	Apparently arrested. Apparently arrested. Cardiac disease. Healed lesion. Arrested. Rapid decline. Rapid decline.
H. B.	M.	W	43	...	Gain	Norm.	Neg.	Hor. L.	6.0	
C. F.	M.	W	21	...	Gain	Sl.	Hemoptysis	Neg.	Hor. L.	6.5	
A. M.	M.	W	32	...	Gain	Sl.	Gastric ulcer (?)	Neg.	Diag. L.	9.0	
F. N.	M.	W	37	...	Gain	Norm.	Pneumonokomosis	Neg.	Diag. L.	13.0	
J. P.	F.	W	26	...	Gain	Norm.	Neg.	Diag. L.	14.0	
J. G.	M.	W	20	+7	Loss	Sl.	Bone	Neg.	Vert. C.	22.0	
W. E.	M.	W	52	+2	Gain	Sl.	Neg.	Vert. C.	31.0	
M. H.	F.	W	33	...	Gain	Sl.	Sl. pos.	Hor. L.	7.0	
I. S.	M.	B	23	...	Gain	Norm.	Sl. pos.	Hor. L.	9.0	
N. W.	F.	W	29	...	Gain	Sl.	Sl. pos.	Diag. L.	10.0	
G. M. C. Q.	F.	W	33	...	Gain	Norm.	Sl. pos.	Diag. L.	14.0	
W. S.	M.	B	31	+6	Gain	Sl.	Sl. pos.	Diag. L.	16.0	
C. T.	M.	W	23	+3	Gain	Sl.	Hemoptysis	Sl. pos.	Diag. C.	26.0	
E. W.	F.	W	21	...	Gain	Norm.	Sl. pos.	Not done	done	
E. B.	F.	W	28	+5	Gain	Norm.	Mod. pos.	Diag. C.	22.0	
W. J.	M.	B	31	+4	Gain	Sl.	Hemoptysis	Mod. pos.	Diag. C.	22.0	
R. F.	F.	W	16	+1	Gain	Norm.	Mod. pos.	Diag. C.	24.0	
S. C.	M.	B	19	+5	Gain	Sl.	Heavy pos.	Diag. L.	18.5	
M. B. A.	F.	W	22	+5	Loss	Sl.	Art. pneumothorax, hemoptysis	Heavy pos.	Diag. C.	27.5	
F. D.	M.	W	46	+5	Loss	Sl.	Heavy pos.	Diag. C.	25.5	Apparently arrested. Apparently arrested. Cardiac disease.
W. K.	M.	W	25	+2	Loss	Sl.	Hemoptysis	Heavy pos.	Diag. C.	23.5	
A. K.	M.	W	24	+6	Gain	Norm.	Heavy pos.	Diag. C.	21.5	
E. T.	F.	W	21	+2	Gain	Sl.	Heavy pos.	Diag. C.	22.0	Healed lesion. Arrested. Rapid decline. Rapid decline.

TABLE V.—MODERATELY ADVANCED "B" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercu- met.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
J.S.	F.	W	27	...	Gain	Sl.	Cardiac hemoptysis	Neg.	Hor. L.	35.0	Apices fibroid.
E.S.	F.	W	33	...	Const.	Sl.	Tub. nephr.	Neg.	Hor. L.	6.5	Apices fibroid.
F.K.	F.	W	25	...	Const.	Sl.	Neg.	Diag. C.	22.0	Bronchiectasis.
E. McK.	F.	W	19	+5	Loss	Sl.	Sl. pos.	Diag. C.	24.5	
M. McC.	F.	W	43	+4	Const.	Sl.	Sl. pos.	Vert. C.	30.0	
M.H.	F.	W	34	+5	Const.	Mod.	Scotiosis	Sl. pos.	Vert. C.	31.0	Bone.
S.K.	M.	W	40	+4	Const.	Sl.	Mod. pos.	Diag. C.	20.0	
T.B.	M.	W	22	...	Gain	Sl.	Empyema (1)	Mod. pos.	Vert. C.	28.5	
							Empyema (2)	Heavy pos.	Diag. C.	26.0	
I.Z.	M.	W	18	+2	Gain	Sl.	Heavy pos.	Diag. L.	23.0	
E. McC.	F.	W	20	+6	Gain	Norm.	Heavy pos.	Diag. L.	24.0	
F.S.	F.	W	16	+5	Gain	Mod.	Heavy pos.	Diag. C.	22.0	
A.S.	F.	W	26	+8	Gain	Sl.	Hemoptysis	Heavy pos.	Diag. C.	24.0	
C.T.	M.	W	47	...	Const.	Sl.	Heavy pos.	Diag. C.	26.0	
N.I.	F.	W	17	+2	Gain	Mod.	Heavy pos.	Diag. C.	28.0	

TABLE VI.—MODERATELY ADVANCED "C" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercu- met.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
M.W.	F.	W	16	...	Gain	Sl.	Bronchitis, mitral stenosis	Neg.	Hor. L.	4.0	Tuberculosis?
D.K.	F.	W	33	+4	Gain	Sl.	SR.	Diag. L.	23.0	Fibroid.
J.P.	M.	W	18	+2	Loss	Sl.	Hemoptysis	HR.	Diag. C.	22.5	
A.O.	F.	W	26	Sl.	Hemoptysis	HR.	Vert. C.	29.5	Pulmonary abscess.
T.S.	M.	W	60	...	Const.	Mod.	Bone tuberculosis, cold abscess	HR.	Vert. C.	30.0	
E.W.	F.	W	53	+7	Gain	Sl.	HR.	Vert. C.	31.0	

bodies producing the reaction. The third negative occurred in a case diagnosed clinically as bronchiectasis and showing a diagonal curve type of sedimentation; sputum has always been negative.

The three slight positive Tubercumet reactions occurred in conjunction with either vertical or diagonal curve types of sedimentation and all in patients who were showing rather marked decline in their general condition.

The remainder of the positive reactions, moderate and heavy, reveal a generally high degree of sedimentation throughout; 2 diagonal line types are 23 and 24 mm. respectively, while the other 6 are of the diagonal curve type.

VI. Moderately Advanced "C" Cases. The single negative Tubercumet reaction in this class occurred in a patient who is in all probability nontuberculous; the physical signs are entirely those of mitral stenosis with secondary pulmonary congestion and chronic bronchitis; the sedimentation was entirely normal.

There was one slight positive Tubercumet reaction; this occurred in a patient with a chronic fibroid tuberculosis, whose sputum was positive once in 17 examinations and whose sedimentation was of the diagonal curve type.

There were no moderate reactions in this group and the heavy reactions occurred in a variety of conditions; 2 of these cases were those of advanced pulmonary tuberculosis; 1 was a case of bone disease and multiple cold abscess in which sputum had always been negative; the remaining one was a case in which the signs were wholly those of pulmonary abscess and sputum was consistently negative. In all these conditions sedimentation was of the diagonal or vertical curve type. We are unable to account for the heavy reaction, either in the case of E. W., where, clinically, the patient was rapidly declining, or the case of A. O., where apparently the lesion was not tuberculous in character.

VII. Far-advanced "A" Cases. The far-advanced "A" group includes 32 cases. The single negative Tubercumet showed a diagonal line sedimentation and was clinically an arrested case, but the time of the test was complicated by an abscess of the right hand.

Of the 4 slight positive reactions, 3 gave diagonal curves, all being clinically active cases and declining steadily. The fourth showed a vertical curve and was a case of Pott's disease and tuberculous kidney with a nephrectomy. There was very little lung involvement here, however; there were 3 continually draining sinuses from the back. Clinically, the case was going down hill, the slight reaction here indicating a gradual loss of body resistance to the disease.

Of the 10 cases with moderate reactions, 1 showed normal sedimentation. Clinically, this case was improving. However, the tests were favorable far out of proportion to clinical findings. Four of the 10 showed diagonal line sedimentations; of these cases, 3 had negative sputa. Of these, 1 was an arrested bone case,

TABLE VII.—FAR-ADVANCED "A" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercumet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
A. McC.	M.	W	43	..+3	Const.	Norm.	Neg.	Diag. L.	16.5	Bone tuberculosis. Bone tuberculosis.
L. C.	F.	W	46	+6	Gain	Sl.	SR.	Diag. C.	25.0	
R. J.	M.	W	17	..	Const.	Sl.	SR.	Diag. C.	26.0	
M. S.	M.	W	34	..	Gain	Sl.	Nephrectomy, Pott's disease	SR.	Vert. C.	27.5	
J. W.	M.	W	24	+5	Gain	Sl.	Hemoptysis	MR.	Diag. C.	23.0	Bone tuberculosis.
W. A.	M.	W	43	..	Const.	Norm.	Thick pleura	MR.	Diag. L.	10.0	
M. M.	M.	W	16	..	Gain	Sl.	MR.	Diag. L.	17.0	
M. C.	F.	W	31	+4	Gain	Norm.	MR.	Diag. L.	17.5	
M. M.	F.	W	23	..	Gain	Norm.	Tb. ankle, tb. larynx	MR.	Diag. L.	18.0	
J. R.	M.	W	39	+2	Gain	Norm.	Hemoptysis, nephritis	MR.	Diag. C.	22.0	
G. T.	M.	W	41	..	Const.	Sl.	Pneumonokoniosis, hemoptysis	MR.	Diag. C.	25.0	Bone tuberculosis.
D. E.	M.	W	23	+2	Gain	Sl.	Nephrothiasis	MR.	Diag. C.	27.0	
G. A.	F.	W	23	+5	Gain	Norm.	MR.	Diag. C.	28.0	
J. M.	M.	W	47	+6	Const.	Norm.	MR.	Vert. C.	29.0	
J. H.	M.	W	28	+4	Gain	Norm.	HR.	Hor. L.	7.5	
D. S.	M.	W	43	+5	Loss	Sl.	Syphilis, hemoptysis	HR.	Diag. L.	14.0	
Dr. L.	M.	W	58	+2	Const.	Norm.	Bronchiectasis	HR.	Diag. L.	21.0	
E. D.	M.	W	49	..	Const.	Norm.	Ischiorectal abscess,	HR.	Diag. C.	19.0	
H. M.	M.	W	30	+5	Const.	Sl.	syphilis	HR.	Diag. C.	21.0	
J. C.	M.	W	45	+4	Gain	Sl.	Pneumonokoniosis	HR.	Diag. C.	22.5	
E. R.	F.	W	22	+5	Const.	Sl.	HR.	Diag. C.	23.0	Bone tuberculosis.
T. L.	M.	W	35	+4	Const.	Sl.	HR.	Diag. C.	23.0	
T. F.	M.	W	41	+2	Loss	Sl.	Syphilis, emphysema	HR.	Diag. C.	23.5	
M. H.	F.	W	32	+4	Const.	Sl.	pneumonokoniosis	HR.	Diag. C.	24.0	
A. A.	M.	W	37	..	Loss	Sl.	HR.	Diag. C.	24.0	
V. K.	M.	W	30	+5	Gain	Norm.	HR.	Diag. C.	25.0	
A. P.	F.	W	20	+6	Gain	Sl.	Hemoptysis	HR.	Diag. C.	25.0	
J. B.	M.	W	21	+6	Gain	Sl.	HR.	Diag. C.	26.0	
H. G.	M.	W	29	+8	Gain	Norm.	HR.	Vert. C.	27.0	
M. M.	F.	W	19	+3	Gain	Sl.	HR.	Diag. C.	27.5	
A. S.	F.	W	25	+9	Gain	Sl.	HR.	Diag. C.	31.0	

another a quiescent lung case and a third showed clinical improvement. The fourth, with a positive sputum, also showed clinical improvement. One case showed a vertical curve type of sedimentation; clinically, the disease was progressing over the patient's resistance.

Seventeen of the cases gave a heavy ring Tubercumet. The one with a horizontal line type was gaining weight, had normal temperature and apparently high resistance. Of the 2 with diagonal line sedimentation, 1 was improving and showed high resistance. However, the other was going down hill and clinically was contradictory to the favorable tests; there is a complication of syphilis, which may have vitiated the results. Of the 13 with diagonal curves, all show moderate activity in keeping with laboratory findings. The one showing a vertical curve has shown a clinical stability out of keeping with the sedimentation curve, although quite in keeping with the heavy resistance indicated by the Tubercumet.

VIII. Far-advanced "B" Cases. Of the 27 cases in the far-advanced "B" class, 2 presented negative Tubercumet reactions. One patient in the last stages of the disease shortly afterward had severe hemoptysis; his sedimentation showed a vertical curve type. The other, however, had a diagonal line sedimentation in spite of a rather down-hill clinical course of an unquestionable tuberculosis.

Two slight positive and 7 moderate positive Tubercumet reactions occurred in this group, all in conjunction with diagonal curve sedimentations of moderate degree. These were all definitely tuberculous cases with the disease well established and active.

Sixteen cases here showed heavy positive Tubercumet reactions with diagonal line sedimentations occurring in the 2 cases which, from a clinical standpoint, were improving. Of the remainder, 11 presented diagonal curve and 3 vertical curve types of sedimentation in some degree of accordance with the extent of the disease.

IX. Far-advanced "C" Cases. In the far-advanced "C" group there are 14 cases, all of which had positive sputa at some time, and involvement of three or more lobes. Of the 3 with negative Tubercumet reactions, 1 has shown a diagonal line sedimentation; this patient had a negative sputum for the year prior to the test and was doing fairly well clinically. The other 2 showed vertical curve sedimentations and clinically were rapidly going down hill.

Of the 3 with slight Tubercumets, 2 had empyema and were rapidly declining; the third had a vertical curve sedimentation in keeping with the clinical activity and loss of weight.

The two cases giving the moderate reaction died subsequent to the tests, following pulmonary hemorrhage.

Of the 6 cases showing heavy ring Tubercumets, 2 did not have blood sedimentations done. Two gave horizontal line types, but

TABLE VIII.—FAR-ADVANCED "B" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercumet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
G. C.	F.	W	35	+6	Loss	Sl.	Pleural effusion, art. pneumothorax	Neg.	Diag. L.	17.0	
H. O. S.	M.	B	37	+5	Loss	Sl.	Neg.	Vert. C.	27.0	
I. G. K.	M.	W	32	+2	Gain	Sl.	SR.	Diag. C.	20.5	
F. B.	F.	W	30	+5	Gain	Sl.	SR.	Diag. C.	25.0	
M. Q.	F.	W	24	+6	Const.	Sl.	Hemoptysis	MR.	Diag. C.	22.0	
T. G.	M.	W	36	+6	Loss	Sl.	Art. pneumothorax, hemoptysis, pneumonokniosis	MR.	Diag. C.	24.0	
G. K.	M.	W	37	+4	Gain	Sl.	Hemoptysis	MR.	Diag. C.	24.5	Bone tuberculosis
H. P.	F.	W	19	+6	Gain	Sl.	MR.	Diag. C.	26.0	
C. D.	M.	W	32	+5	Loss	Sl.	Hemoptysis, pneumonokniosis	MR.	Diag. C.	26.5	
L. B.	F.	W	23	+2	Loss	Sl.	Hemoptysis	MR.	Diag. C.	28.0	
W. H.	M.	B	31	+8	Loss	Sl.	MR.	Diag. C.	29.0	
R. R.	M.	W	41	+3	Gain	Norm.	HR.	Diag. L.	11.0	
R. K.	M.	W	23	+2	Loss	Norm.	Hemoptysis, ischio-rectal abs.	HR.	Diag. L.	12.0	
A. McE.	M.	W	50	+8	Gain	Sl.	HR.	Diag. C.	21.0	
F. W.	M.	W	34	+5	Loss	Sl.	Hemoptysis	HR.	Diag. C.	21.0	
A. Y.	M.	W	14	+2	Const.	Sl.	Pleural effusion	HR.	Diag. C.	22.5	
F. C.	F.	W	29	+4	Gain	Sl.	Hemoptysis	HR.	Diag. C.	23.0	
A. M.	M.	W	42	+5	Const.	Sl.	Hemoptysis	HR.	Diag. C.	23.0	
B. DeP.	M.	W	46	+2	Loss	Sl.	Hemoptysis, pneumonokniosis	HR.	Diag. C.	23.5	
B. N.	F.	W	50	+4	Loss	Sl.	HR.	Diag. C.	24.0	
J. G.	M.	W	23	+5	Loss	Sl.	Hemoptysis, cold abscess	HR.	Diag. C.	25.0	
A. K.	M.	W	42	+2	Gain	Sl.	Syphilis	HR.	Diag. C.	25.0	
M. G.	F.	W	31	+7	Loss	Sl.	Hemoptysis, cervical adenitis	HR.	Diag. C.	26.0	
E. N.	F.	W	38	+4	Gain	Sl.	Hemoptysis	HR.	Diag. C.	27.0	
J. C.	M.	W	42	+7	Gain	Sl.	HR.	Vert. C.	28.0	
F. S.	M.	W	32	+7	Gain	Sl.	Syphilis	HR.	Vert. C.	28.0	
A. S.	F.	W	41	+3	Loss	Sl.	HR.	Vert. C.	35.0	

TABLE IX.—FAR-ADVANCED "C" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercuemet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
L. DeJ.	M.	W	30	..	Loss	Sl.	Hemoptysis	Neg.	Diag. L.	16.5	
S. H.	M.	W	58	+5	Loss	Sl.	Neg.	Vert. C.	28.5	
A. J.	F.	B	23	+2	Loss	Mod.	Neg.	Vert. C.	33.0	
M. Y.	M.	W	37	+2	Loss	Sl.	SR.	Diag. C.	27.5	
W. R.	M.	W	16	+6	Gain	Sl.	Empyema	SR.	Diag. C.	28.0	
M. B.	F.	W	15	..	Loss	Sl.	Hemoptysis	SR.	Vert. C.	29.5	
J. D.	M.	W	26	+7	Loss	Mod.	Empyema	MR.	Not done		Died.
J. W.	M.	W	45	+3	Gain	Sl.	MR.	Diag. C.	29.0	Died.
S. J.	M.	B	28	+5	Loss	Mod.	Nephritis	HR.	Not done		
M. K.	M.	W	38	+2	Gain	Sl.	Hemoptysis	HR.	Not done		
J. G.	M.	W	26	+7	Loss	Sl.	Nephritis	HR.	Hor. L.	4.0	
R. McC.	M.	W	23	+4	Loss	Sl.	Hemoptysis; hereditary syphilis	HR.	Hor. L.	8.0	Neg. 18 months.
M. G.	M.	W	49	+6	Loss	Sl.	HR.	Diag. C.	30.0	
E. O.	M.	W	22	+4	Gain	Sl.	Pleural effusion	HR.	Vert. C.	29.5	

both of these patients were doing very poorly clinically, a fact which seems to contradict the test findings. One of these cases was complicated by syphilis. Of the remainder, 1 gave a diagonal curve and the other a vertical curve sedimentation; both had started a clinical down-hill course but not to an overwhelming extent.

Summary. Review of the 147 cases here presented shows that in 136 instances the combinations of the sedimentation and serum test results give, when interpreted in the light of the previously constructed scheme of possibilities, pictures which closely approximate those determinable by the usual methods of diagnosis (symptomatology, physical signs, sputum examination, Roentgen ray and so forth). In 11 cases only are the test findings at variance with the clinical condition as indicated by such methods. On analysis of these 11 cases it is found that 3 negative Tubercumet reactions (2 with diagonal line and 1 with vertical curve sedimentations) occurred in patients with apparently definite active tuberculosis and in whom there was no evidence of a sharp decline in condition; of these, however, 1, a Philippino, has always had negative sputum and is a possible case of mycotic infection. Two moderate positive Tubercumet reactions, in conjunction with horizontal and diagonal line sedimentation curves, respectively, occurred in patients with definitely advancing tuberculosis. Four patients presenting heavy positive Tubercumet reactions with horizontal or diagonal line sedimentation curves were thought to be quite definitely in the period of declining resistance and advancing infection. However, 1 of these now has negative sputum and is showing no signs of pathologic activity in the lungs, while another was recently discharged as "quiescent." Two cases had heavy positive reactions with vertical curve sedimentations in spite of the fact that there was, especially in 1 case, considerable advance in the disease process.

It is worthy of note here that the 5 patients of this series who had a definite syphilitic infection (evidenced by positive serological findings), all had heavy positive Tubercumet reactions. Furthermore, 4 of these are included in the 11 cases, the interpretations of whose test results conflict with the clinical findings.

Conclusions. We do not believe that one is truly justified in drawing conclusions as to the worth of this method from this single series of observations. The several chances for error in the individual tests and in the interpretation of the combined results, the comparatively small number of cases worked upon to date and the lack of basic knowledge of sedimentation and serum reaction phenomena preclude positive assertions. However, the fact is encouraging, that in this single series there is a rather high degree of correlation between the clinical condition of the individual patients and the results of the tests as interpreted in the arbitrarily constructed scheme here presented. The basic principles of the

sedimentation and Tubercumet reactions, the relation of syphilis to the serum reaction, and so forth, present subjects for further investigation.

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THE ARTIFICIAL PRODUCTION OF PUNCTATE BASOPHILIA AND RETICULATION IN ERYTHROCYTES.

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FROM the time Ehrlich (1885) noted the three distinct basophilic conditions in erythrocytes, controversies have waged on their character and significance; but for many years the trend of opinion has been toward the view that punctate basophilia, diffuse polychromasia and reticulation are expressions of the same process.

Cesaris-Demel (1907) concluded that punctate basophilia and reticulation are identical, and Key (1921) agrees that the basophilic substance in the three conditions is the same. Brookfield (1928) believes that the stippled cells in lead poisoning are immature cells (reticulocytes and polychromatic cells) altered by the toxic action of lead. His results tend to confirm the work of Hawes (1909) and Key (1924) in which the close numerical relationship between stippled and polychromatic cells and reticulocytes was definitely established.

The nature of the staining substance is still undetermined, nor has any explanation been offered as to why the different appearances occur. Pappenheim (1907) and Biondi (1908) independently propounded the view that the stainable substance is a dye precipitate upon the surface of the lipid membrane, but later, Pappenheim (1919) rather altered this idea, and suggested that the lipid component of the spongoplasm was the reacting substance.

That the substance is not chromatinic is beyond doubt. The staining reaction with methylene blue-cosin preparations and with methyl-green pyronin, the occasional appearance of the condition in normally nucleated erythrocytes, and the fact that none of

the conditions is visible by dark-ground illumination or ultraviolet light are among the arguments against punctate basophilia, polychromasia and reticulation being nuclear in origin.

Gruner (1913) suggested that the reticular substance is not nuclear but plasmatic in character because in embryos and young animals its abundance is not associated with the appearances of changes in the nucleus. I have confirmed this observation in cases of Addison's anemia during normoblastic crises, in von Jaksch's anemia and in myeloid leukemia. In these diseases there does not appear to be any relationship between the younger normoblasts and the older normoblasts and the amount of reticular substance.

The present work is an attempt to elucidate these problems. The fact that hemoglobin gives a characteristic reaction with benzidin and hydrogen peroxid was utilized to the exclusion of all other stains. Blood films were made on 3 by 1 microscope slides and allowed to dry in the air before treatment. By altering the quantities of the reagents,* it is possible to disturb the apparent homogeneity of the erythrocyte. For the better appreciation of the early effects we will take the final results first. Fig. 1 is a photomicrograph of erythrocytes from which the hemoglobin has been more or less completely discharged. Benzidin in alcohol and hydrogen peroxid were used in such strengths that when flooded on to the film a greenish precipitate was immediately produced from the released hemoglobin and floated to the surface. The reaction was allowed to continue for twenty minutes. If the corpuscles in the figure be examined with a hand lens an irregular meshwork is seen and the spaces between the strands have the appearance of pores. The outline of the cells is irregular but the mean diameter is increased. The probable sequence of events is that the lipid membrane has been oxidized and dissolved, and a slow fixation has brought into evidence a spongy stroma through the interstices of which the reagents have penetrated. Reaction between the benzidin and hydrogen peroxid and hemoglobin has taken place with solution and escape of the end product. Having seen the end result, all kinds of patterns, depending upon the varying degrees of penetration of the envelope and the amount of hemoglobin released, would appear possible. This is, in fact, true. Every type of punctate basophilia and reticulation may be duplicated.

Fig. 2 is an example of punctate basophilia of the fine type. If the cells are examined with a lens it will be apparent that the reaction has not progressed to the stage of Fig. 1. There are areas in which the granules are sharply defined but in others they are blurred in outline, suggesting that the hemoglobin has been reached but different stages of the reaction taken place.

* The reagents are benzidin 0.01 per cent in 80 per cent alcohol and hydrogen peroxid.

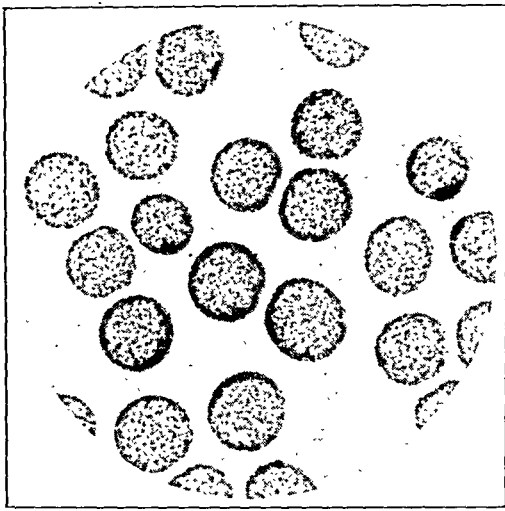


FIG. 1.—Erythrocytes showing spongioplasm after the lipoid membrane has been altered or dissolved. $\times 1000$.

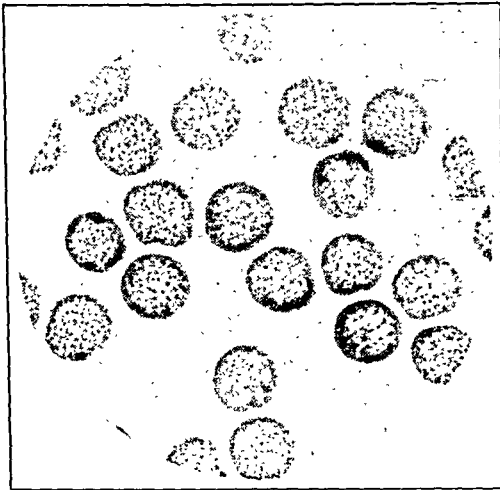


FIG. 2.—Erythrocytes showing finely granular punctate basophilia. $\times 1000$.

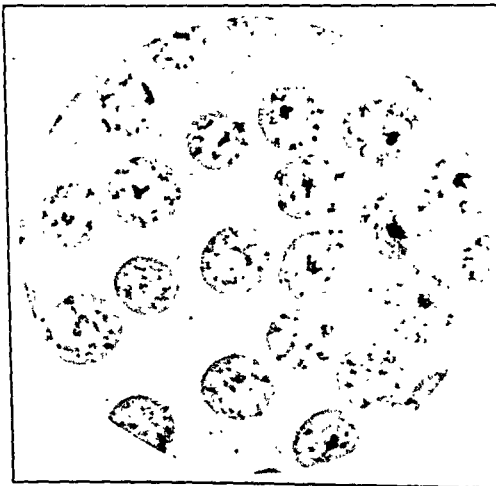


FIG. 3.—The clumped form of punctate basophilia showing granules of irregular shape. $\times 1000$.

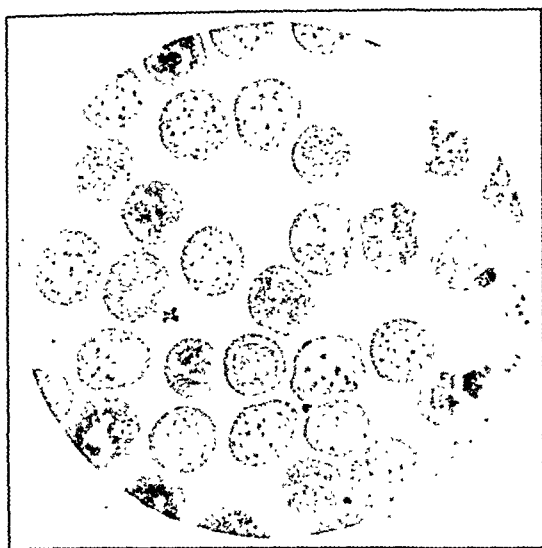


FIG. 4.—Punctate basophilic reticulation and diffuse polychromasia (x). $\times 1000$.

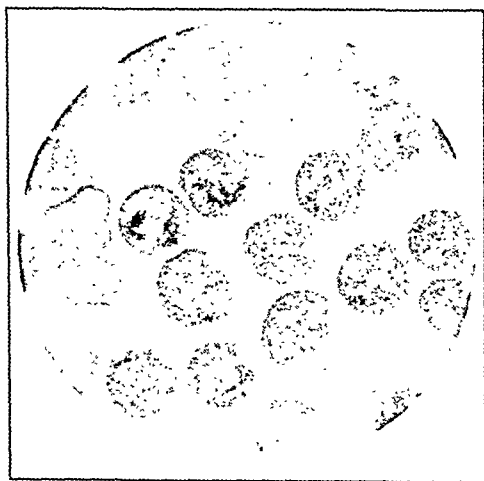


FIG. 5.—The bar form of reticulation. $\times 1000$.

The granules may be fine, as in this figure, or coarse, as in some of the cells in Fig. 4, or they may be irregular in shape and aggregated into small clusters, as in Fig. 3.

At a further stage the hemoglobin has escaped through the pores and bridged over intervening strands of the stroma. Areas have coalesced in an irregular manner and the appearance of reticulation results, as shown in some of the cells in Fig. 4. Though the "granulofilamentous" picture characteristic of the vital staining methods is not reproduced here, it is obvious that no fundamental difference could be necessary for its production.

As may be imagined, it is difficult to get the granulofilamentous form of reticulation, but I have done so in an odd erythrocyte.

All the forms of reticulation described by Brookfield (1928) from the unfragmented reticulum to the bar form may be reproduced. Fig. 5 is an example of the bar form. The reticulocytes in Fig. 4 suggest that the next stage must be diffuse polychromasia. The cell marked *X* in Fig. 4 illustrates the condition up to a point, but there is a rim of unaffected material around the central stained area. This is probably due to the time given for the reaction being too short.

Summary.—This preliminary note is merely intended to place on record the fact that punctate basophilia, diffuse polychromasia and reticulation may be produced in any erythrocyte. The time is not opportune to enter into the discussion which these results open up, but two deductions may, I think, be made. The first, that with our previous knowledge of the staining reactions, the above results strengthen the belief that the stainable substance is not nuclear in character, but is probably a hemoglobin compound, and that the three basophilic conditions of the erythrocyte are qualitatively the same and vary only in degree or method of production.

The second deduction is that the conditions when obtained by the usual staining methods would point to increased permeability or a defect in the lipoid envelope of the erythrocyte. There may be, and probably is, a close relationship between punctate basophilia, diffuse polychromasia and reticulation and immaturity.

NOTE.—I must take this opportunity to express my thanks to my friend, C. F. Hill, for his invaluable assistance with the photomicrographs.

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POLIOMYELITIS.

ITS PRE-PARALYTIC PERIOD WITH RESULTS OF SERUM THERAPY.* †

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THIS paper is the report of 126 cases of poliomyelitis seen in the pre-paralytic stage and treated by the intraspinal injection of human immune or convalescent serum and in few instances, by non-specific horse serum.

These cases occurred in the city of Syracuse or the surrounding territory during 1921 to 1926 inclusive, and were all seen by this observer in the capacity of private consultant or as consultant to the Syracuse Department of Health. This series is the largest number of such cases hitherto reported. It is felt that by it the value of intraspinal administration of serum to the early case is more definitely established, and, with our present knowledge of the disease is also demonstrated to be a proper therapeutic procedure. In the hands of this observer, such treatment in early cases of poliomyelitis has been apparently attended by most gratifying success and there is now no doubt in his mind as to its indication and value. Unfortunately, there are those who still think otherwise and controversy persists.

Surely the interpretation of results of any therapeutic procedure is often attended by difficulty. If such procedure were directed against a condition which, untreated, is characterized by 100 per cent mortality or 100 per cent development of uniform and characteristic sequelæ, then judgment would indeed be a simple matter. This, of course, is not true in poliomyelitis, as here the greatest variation exists in the severity of the case and in extent and distribution of the paralytic sequelæ, which range from the mildest type with only a simple muscle-group involvement to the fulminating tragic bulbar type, and to the more extensive paralyzes of one or more extremities, 20 per cent of which end fatally. And then to make determination still more difficult, it may be that there are cases which do not develop paralysis at all and constitute the so-called abortive, evanescent, or nonparalytic type.

Generally speaking, and with the exception of the fulminating bulbar case, the pre-paralytic or febrile period is quite similar in all, and no one seeing a patient in this early stage can accurately prophesy the subsequent development. Consequently, it is here

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in this so-called abortive type that we find the great stumbling-block to satisfactory discussion and determination.

Nonparalytic Types. There are no accurate statistics available as the existence of such, but it is undoubtedly true that in the pandemic of 1916 such cases were seen with a roughly estimated incidence from 25 to 50 per cent. However, it is now felt that the percentage was then, and still is, greatly overestimated, and that its diagnosis was one most often made on only conjecture and hearsay. Abortive or nonparalytic cases, however, were definitely recognized in 1916 in Syracuse and vicinity, but only in small numbers and since then have been strikingly absent. In the writer's complete series of 340 cases since 1916, only 4 such have come to his attention, and, with inquiries among many physicians, it must be concluded that they are rare. Certainly, it cannot be that all the favorable cases of this treatment series were abortive cases and coincidentally treated and yet that is an argument that has to be met. This may be done quite conclusively by the fact that during the same five-year period 210 cases were also seen by this observer in the early hours of paralysis and in all of them the history of the same characteristic symptoms of the preparalytic period was obtained. Surely, were abortive or nonparalytic types numerically prevalent, their presence would have been quickly remarked, certainly in more than 4 instances.

Extent of Paralytic Involvement in Direct Ratio to Pre-paralytic Severity. This series may possibly represent some nonparalytic cases, but it is believed that most of the 126 were potentially true paralytic types and in most of, if not all, the 93 recoveries the therapy instituted prevented crippling sequelæ of variable degree, and some fatalities. Furthermore, it can be fairly said that many of this number represented the severer types of the disease, as the greater severity of their early symptomatology gave rise to the more immediate suspicion of the nature of the process and to the earlier diagnosis and treatment. Certainly, in the series of paralytic cases diagnosed only at the paralytic stage, it is quite evident that the extent of paralytic development was most often in direct ratio to the severity of the pre-paralytic symptoms.

Serum to the Paralyzed Case. Unfavorable opinion of serum therapy has been greatly engendered by the delayed and apparently unsuccessful administration in the presence of paralysis. It is then too late and, of course, unsuccessful. Certainly, paralysis once established cannot be greatly influenced by intraspinal serum and unless we have a case very early in this paralytic period, with continuing fever and persisting high cellular reaction in the spinal fluid, serum should not be given.

Early Access to Cases. In 1924, 133 cases with 12 deaths occurred in the city of Syracuse. Sixty-one were diagnosed in the pre-paralytic stage and given serum. Of these, 50 did not develop paralysis. This is pointed to with pride, but with the possible exception of 14

bulbar cases, all the others might have likewise been so diagnosed and treated. The early access to these cases was accomplished by newspaper publicity with the careful and conservative description to the public of the early symptoms, the advice to call the doctor immediately, and by the maintenance of consulting diagnosticians with available convalescent serum. It might be remarked that the death rate in this 1924 series was 9 per cent as compared with Syracuse figures of 28 per cent in 1916, 24 per cent in 1922, and 21 per cent in 1926. This, of course, is not alone conclusive argument for early serum treatment, but it must be given some consideration, as in no other series was there such a high percentage of early diagnoses.

Diagnosis. It is to be recalled that poliomyelitis is an acute infectious disease of the central nervous system and characterized by a very typical febrile period averaging three days in duration. This, in reality, is the active disease, although termed the pre-paralytic period. It ends quite abruptly with the appearance of paralysis of extremities or involvement of the motor cranial nerves and then, after a few hours (averaging twenty-four) for the complete institution of paralysis, the active disease is in reality over, and it becomes in comparison a passive problem in orthopedics.

The serum therapy of poliomyelitis necessitates its early diagnosis, that is, diagnosis in its pre-paralytic, febrile, or active period. This sometimes in sporadic cases may offer a perplexing problem to the attending physician, or even to the expert diagnostician. But rarely so. In former years diagnosis was made only on the appearance of paralysis, but with our present knowledge, there is certainly little excuse for missing cases, and in epidemic times it seems hardly justifiable that a pre-paralytic case should ever be mistaken.

It seems generally accepted that this disease is a systemic infection, but in the conception of this observer, it presents clearly a distinctive infection of the central nervous system with a pre-paralytic invasion of the meninges and a subsequent myelitis with its accompanying paralysis. It is indeed difficult for him to see it in the light of a systemic disease, as we ordinarily accept that classification.

Dromedary Type. However, as evidence of the possible systemic nature we should consider the dromedary type with an approximate incidence of 50 per cent. It is called dromedary because of the two humps or rises of temperature. Two to four days before the real beginning of the recognizable neurologic symptoms there may be a forty-eight-hour illness with fever, malaise, headache and vomiting. There is no rigidity of the neck, no tremor, and the general picture is that of an intestinal infection. The patient is usually in bed a day or two, then is apparently normal, until two to four days later, there is then developed the characteristic meningeal pre-paralytic picture. The initial "hump" of temperature may be interpreted as

evidence of preliminary intestinal infection with probable blood-stream invasion, a systemic disease. The subsequent, or second hump, representing its localization in the meninges and the initiation of the actual neurologic process. This type is also of especial interest in the consideration of the so-called abortive types. It is the author's opinion that there are many cases of this initial two-day illness which stop there and do not proceed to the further extension in the meninges. These then may constitute abortive cases, but they are never recognized as pre-paralytic poliomyelitis or so treated. The spinal fluid in three such cases has been examined by him and found entirely negative.

Symptoms and Signs. The pre-paralytic picture presents as a distinct clinical entity with symptoms definitely those of a mild meningitis; headache, tremor, and stiff neck constituting an outstanding triad.

Objective and subjective signs may be listed together as follows in order of importance:

1. *Fever.* Never high, with an average of 102° F.
2. *Headache.* Is severe; most frequently general, but may be nuchal and sometimes may be absent, but then replaced by severe back pain.
3. *Rigidity of the Neck.* Distinct resistance to anterior flexion. Rarely is there retraction and never lateral limitation.
4. *Tremor.* Fine trembling of lips and hands, especially on movement as when taking a glass of water. There may be also coarse twitching in sleep.
5. *Apathy.* The patients are mildly indifferent and drowsy—never comatose and are perfectly bright and alert when aroused, but then are sometimes irritable.
6. *Vomiting.* Once or twice on the first day, but rarely is it persistent or severe. It should be mentioned that vomiting is often severe as an initial symptom in the bulbar types.
7. *Retention of Urine.* When questioned, the mother often remarks a twelve- to twenty-hour period without urination; it never demands catheterization.

8. *Constipation.* It is almost uniformly present.

9. *Sweating.* This is usually seen as beading about the lips and neck, and is rarely profuse.

During this stage all movements of extremities are freely made and there is no great change in reflex or sensory status. It is to be forcefully emphasized that coma and convulsions, severe vomiting, diarrhea, chills and hyperpyrexia have never been observed by the author, and in his opinion, do not occur. In the bulbar type of case the pre-paralytic period is not so consistent and is much shorter in duration. In many such, there is difficulty in swallowing almost from the onset.

Spinal Fluid. With the exception of the bulbar and encephalitic types, this clinical picture is almost pathognomonic and is readily confirmed by lumbar puncture and here we find actual proof of the underlying meningeal pathology. This is in the pleocytosis of the fluid, the average count being 350 to the cubic millimeter. The pressure is slightly increased, and the fluid grossly shows varying degrees of turbidity. A 200 count seems, at first glance, as a clear fluid, but a distinct shimmer can be made out when carefully compared with the normal tube; with 350 cells there is a slight opalescence; with 500 a distinct opalescence, and at 1000 there is turbidity, indistinguishable from that of a suppurative meningitis. Microscopically, the type and proportion of cells varies; in severe cases in the first twenty-four hours the "polys" may predominate, but later the lymphocyte and an ependymal cell are the prevailing forms. Globulin or protein is, of course, consistently increased. The average fluid findings may be simulated in tuberculous, luetic and mumps meningitis, but such rarely give rise to confusion.

It is urged that fluid examination be made at the bedside. The number of cells can be immediately determined and the increase of globulin can be ascertained by the simple alcoholic precipitation test. Then, with such fluid confirmation, treatment can be instituted immediately. It is a great mistake to send the fluid to a nearby or distant laboratory and then await their report for a diagnosis of poliomyelitis, such delay may well be fatal.

Again, it is emphasized that poliomyelitis can be and should be diagnosed in this stage and before the ensuing paralysis makes it clear to all. With the development of paralysis, the fluid coincidentally shows the rapid disappearance of cells and in three or four days it is cell-free but with some persisting increase of protein. Hence, in older textbooks, the spinal fluids were reported as not remarkable, this, of course, being due to the fact that they were the fluids only from the paralyzed cases, with a then inactive pathology in the meninges.

Serum Treatment. Experimentally, the neutralizing or protecting power of human immune serum has been conclusively proved. In 1910, Levaditi and Landsteiner, Flexner and Lewis, and others demonstrated that 1 cc. of human or monkey convalescent serum rubbed up with 0.3 cc. of cord suspension, a fatal dose of virus, would neutralize that virus *in vitro*, in that this combined intradural implantation in monkeys was not followed by the otherwise usual development of the disease. Also, twenty-four hours after the intradural injection of a fatal dose of virus, 10 cc. of convalescent serum given intraspinally likewise protected the monkey from paralysis. Injections of serum given later than twenty-four hours were not so successful in aborting the process. These experimental results were at once utilized as a basis of serum therapy in man.

The method is as follows: Blood is collected with aseptic pre-

caution from individuals who have recovered from the disease preferably within a four-year period. However, donors, with their paralyses of twenty years' standing, were also used, and without any apparent difference in results. The serum is carefully separated and inactivated; to it may be added as a preservative 0.2 per cent tri-cresol. In Syracuse, this serum was obtained by advertising and paying for it. Two hundred and fifty cubic centimeters were taken from adult individuals, and from this 100 cc. of clear serum were usually obtainable.

Its administration in this series has been entirely intraspinally. It is given by gravity after the removal of a greater amount of fluid, but drainage is continued until definite nuchal pain is complained of. The amounts of serum given vary from 10 to 25 cc., according to the size and age of individual. It is now believed that one mistake of the earlier cases was too small dosage; 10 cc. in an infant is not too large, and 25 cc. should be given to the vigorous adult.

The opportunity is taken here to emphasize the fact that serum treatment necessitates lumbar puncture, and, although in the hands of the experienced, a simple procedure, it can become a very disturbing and distressing one in the hands of others. The man who, with grim determination, proceeds to make a colander of the back of a struggling and suffering child may well produce much more harm than his serum can do good. The importance of proper position of the patient, the preliminary use of novocain and a small 19- to 20-gauge lumbar puncture needle, sharp and free from rust, needs hardly to be mentioned. A child or adult should rarely be hurt with lumbar puncture. Anesthetics are seldom necessary and are advised against, as it is believed that anesthesia renders the nerve cells less resistant to invasion of the virus.

Reactions. Mild reactions may follow the administration of human convalescent serum. This is in the nature of increased elevation of temperature four to eight hours after, and the accentuation of headache, back pains and restlessness. Such reactions are never dangerous and no untoward effect has ever been noted by this observer, however, it is strongly urged that the pain and restlessness be controlled by opiates—*the child must be kept quiet!* Also, the importance of proper nursing and careful observation cannot be overemphasized. Temperature should be taken every two hours. From the twelfth to twentieth hours after serum, observations should be made every hour.

Second Serum Administration. The decision for repeat of serum is often a delicate one and much depends upon the accuracy of observation. In this series, where possible, serum was repeated when temperature observations at the eighteenth to twentieth hour showed fever of 101° F. or more. The spinal fluid is usually cloudy from the first serum and is no true index of activity. However, some observers advise the serum administration only as the cell counts are 200 or over. The determination by temperature is considered the

safest determination. This decision should mainly rest with the consultant, who should again see the patient at this period. There is rarely the opportunity of a third dose as the patient is either paralyzed or recovered after a second. Again, the attending physician must watch his case. The time element is short, the potentialities are grave and his responsibility is great. Temporization, with "waiting till tomorrow" is often disastrous.

Results. In 1916, during the hectic days of that epidemic, 36 early cases were treated with intraspinal serum by this observer; 19 cases cleared without paralysis. Cases were then poorly checked and often only seen once. Sometimes, due to the lack of immediately available human convalescent serum, normal human, pneumococcic, and normal horse serum were given, and given mainly on an empirical basis, but surprisingly, often with equally favorable results. These nonspecific results and the then reported high incidence of the abortive case made analysis difficult and the author, with other field workers, was somewhat guarded in his opinion feeling that such recoveries might be coincidental, but since that time and mainly by the experience here presented, he is now convinced as to the value of serum treatment and earnestly advises it as the proper procedure in the early period of this disease.

The table of 126 cases is here presented for appraisal. They are grouped by year, 1921 to 1926 inclusive, and for each year the cases are tabulated in order of the duration hour arranged with the clinical findings, fluid findings, serum administered and results.

It is to be noted that there are comparatively few paralyses in those cases seen in the first twenty-four hours from onset. Of these 126 cases, there were 8 deaths, as follows:

Reports of Fatal Cases. CASE 6.—Jack F., aged four and a half years, received 8 cc. of human immune serum at twenty hours. A second dose was urged at forty-four hours, but permission was refused. On the third day, in the presence of beginning paralysis, serum was then repeated at the request of the parents and attending physician. This was done under an anesthetic, also at their request. The child died the following day with paralysis of all extremities, a cervical respiratory death.

CASE 7.—Ellwyn C., aged seventeen years, seen at twenty-six hours, received 15 cc. human immune serum; fourteen hours later beginning paralysis of uppers appeared and no additional serum was given. Paralysis gradually extended to all extremities with cervical respiratory death on the fifth day. This was a frank disappointment. It is of interest to note that this patient was a muscular truck driver and determinedly kept driving through a cold, rainy day during the first twelve hours of illness.

CASE 64.—Andrew D., aged sixteen years, was seen at thirty hours with a second dose given at fifty-four hours. The interesting finding here was an absence of the usual reaction to the first serum as shown by the low cells in the second puncture. This boy was, likewise, a great disappointment, as two doses of serum were given in satisfactory amounts, at proper intervals and without apparent benefit.

POLIOMYELITIS—PREPARALYTIC STAGE.
(Results of Intraspinal Serum Therapy.)

1921
15 Cases reported in Syracuse—2 deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Dura- tion.	Temp.	Pulse.	Head- ache.	Neck.	Tremor.	Apathy.	Spinal fluid.				Serum.	Results.
													Cells.	Polys.	Lympho.	Protein.		
1	Oct. 12	Stephen M.	Syracuse	Luke	15	5 hrs.	103	—	+++	+++	+++	+++	350	57%	38%	+++	12 cc. Pn.	No paralysis.
2	Sept. 28	Donald G.	Syracuse	Lawless	5	26 hrs.	104	120	++	+++	++	+++	210	—	90%	+++	6 cc. Pn.	No paralysis.

1922
46 Cases in Syracuse—11 Deaths.

3	Sept. 21	James W.	Syracuse	Mesick	4	14 hrs.	102.5	—	+	+++	+++	+++	20	Lymphocytosis	+++	+++	15 cc. H.I.	No paralysis.
4	Sept. 2	Laura R.	Fabius	Gossner	15	15 hrs.	101	100	++	+++	+	+	50	Lymphocytosis	+++	+++	15 cc. H.I.	No paralysis.
5	Sept. 12	Henry M.	Liverpool	Platner	4	20 hrs.	103	152	+++	+++	+++	+++	320	—	—	+++	15 cc. Pn.	No paralysis.
6	Oct. 11	Jack F. §	Syracuse	Wynkoop	4½	20 hrs.	102.6	136	+++	+++	+++	+++	500	95%	95%	+++	{ 8 cc. H.I.	Extensive paralysis §
7	Oct. 19	Ellwyn C. §	Syracuse	Harter	17	68 hrs.	102	100	+++	+++	+++	+++	200	—	—	+++	{ 8 cc. H.I.	Extensive paralysis §
8	Sept. 11	Dorothy K.	Syracuse	Bamford	6	40 hrs.	102	—	+++	+++	+++	+++	360	—	—	+++	15 cc. H.I.	Extensive paralysis §
9	Oct. 9	James W.	Apulia	Padgett	13	34 hrs.	101	136	+++	+++	+++	+++	220	—	—	+++	10 cc. H.I.	No paralysis.
10	Aug. 20	Robert G.	Eastwood	Seagird	6	36 hrs.	103	—	+++	+++	+++	+++	160	—	—	+++	10 cc. H.I.	Weakness right quadriceps.*
11	Sept. 8	Josephine H.	Syracuse	Mitchell	2	36 hrs.	101	—	+++	+++	+++	+++	250	—	—	+++	15 cc. Pn.	Paralysis right shoulder.*
12	May 21	Dwight C. †	Syracuse	Sharkey	7	36 hrs.	102.4	140	+++	+++	+++	+++	140	—	—	+++	15 cc. Pn.	No paralysis.
13	Oct. 14	Hazel D.	Fabius	Gossner	10	56 hrs.	101.4	112	+	+++	+++	+++	Cloudy	99%	99%	+++	{ 12 cc. H.I.	Paralysis both arms, one lower. †
14	Sept. 13	James H.	Fabius	Gossner	12	40 hrs.	101.3	104	+++	+++	+++	+++	250	—	—	+++	16 cc. H.I.	No paralysis.
15	Oct. 17	Leslie C.	Apulia	Padgett	16	67 hrs.	101.8	130	+	+++	+++	+++	160	Fluid—Low pressure	—	+++	{ 15 cc. Pn.	No paralysis.
						48 hrs.	101	194	+++	+++	+++	+++	90	—	—	+++	12 cc. H.I.	No paralysis.

1923
8 Cases in Syracuse—1 death.

16	Aug. 8	Charles B.	Syracuse	Wood	5	20 hrs.	102.1	138	+++	+++	+++	+++	760	94%	6%	+++	10 cc. Pn.	No paralysis.
17	Sept. 9	John G.	Liverpool	Platner	6	32 hrs.	102	—	++	+++	+++	+++	160	—	—	+++	10 cc. Pn.	No paralysis.

Pn.—Pneumococcus serum
H. I.—Human immune.

*—Muscular weakness—clearing in six months—13 cases.
†—Paralysis of moderate degree—residual in one extremity—9 cases.
‡—Severe paralysis with permanent involvement of more than one extremity—4 cases.
§—Deaths in italics—8 cases.

83 cases cleared without paralysis.
46 cases seen within the first twenty-four hours.

POLIOMYELITIS—PREPARALYTIC STAGE.—(Continued.)

1924
133 Cases in Syracuse—12 Deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Dura- tion.	Temp.	Pulse.	Head- ache.	Neck.	Tremor.	Apathy.	Spinal Fluid.				Serum.	Results.
													Cells.	Polys.	Lympho.	Protein.		
18	June 29	Donald A.	Syracuse	Palmer	9	5 hrs.	102	130	++	++	++	+	620	60%	40%	+++	10 cc. Pn.	No paralysis.
19	Aug. 20	Eugene H.	Manlius	Curtiss	11	25 hrs.	101	120	++	++	++	++	Cloudy	100%	90%	—	10 cc. Pn.	(Serum react. ++).
20	Aug. 20	Dorothy W.*	Syracuse	Ransom	6	6 hrs.	103.2	—	++	++	++	++	240	—	90%	+++	10 cc. Pn.	No paralysis.
21	Aug. 5	Chas. W.	Syracuse	Ooombs	9	6 hrs.	102	140	++	++	++	++	350	—	—	+++	10 cc. Pn.	Sl. weakness right quadriceps.*
22	Sept. 17	Paul M.	Syracuse	Caye	5	32 hrs.	102.2	136	++	++	++	+	300	90%	10%	+++	10 cc. H.I.	No paralysis.
23	Aug. 6	Raymond S.	Syracuse	Ayling	4	10 hrs.	101	130	++	++	++	++	Bloody	—	—	—	10 cc. Pn.	(Serum react. ++).
24	Aug. 24	Robt. F.	Syracuse	Babcock	2	10 hrs.	100.8	134	++	++	+	+	60	—	Lymphocytosis	+++	10 cc. H.I.	No paralysis.
25	Aug. 11	Basil R.†	Syracuse	Cave	10	12 hrs.	102	140	++	++	++	++	65	15%	25%	+++	10 cc. H.I.	No paralysis.
26	Aug. 21	Mary E.	E. Syracuse	Marsh	7	32 hrs.	101.4	120	++	++	++	++	600	20%	80%	+++	10 cc. H.I.	No paralysis.
27	Aug. 26	Elizabeth W.	E. Syracuse	Lawless	16	12 hrs.	Temp.	reporte as normal and boy	++	++	++	++	—	—	103	+++	10 cc. Pn.	Extensive descending paralysis.†
28	Aug. 30	Carl G. H.	E. Syracuse	Snyder	4	12 hrs.	104	144	++	++	++	++	220	—	—	+++	12 cc. H.I.	Survival.
29	July 19	William S.	Syracuse	Blodgett	5	12 hrs.	101	102	++	++	++	++	190	—	+90%	+++	15 cc. H.I.	No paralysis.
30	Aug. 5	Irma C.	Syracuse	Broughton	13	15 hrs.	100.2	124	++	++	++	++	967	—	—	+++	6 cc. Pn.	No paralysis.
31	Aug. 4	Wm. L.	Eastwood	Marsh	7	16 hrs.	102	128	++	++	++	++	320	20%	80%	+++	10 cc. H.I.	No paralysis.
32	Aug. 16	Rose McD.	Syracuse	Larned	4	36 hrs.	102	100	++	++	++	++	280	90%	85%	+++	10 cc. H.I.	No paralysis.
33	Aug. 25	James H.	Syracuse	Wood	6	18 hrs.	101	120	++	++	++	++	1380	—	—	+++	8 cc. Pn.	No paralysis.
34	July 26	Bernard G.	E. Syracuse	Seagfrid	8	38 hrs.	101.2	100	++	++	++	++	Turbid	95%	—	+++	8 cc. Pn.	(Serum react. +).
35	July 30	Carl G.	E. Syracuse	Seagfrid	13	20 hrs.	101.4	130	++	++	++	++	120	—	90%	+++	12 cc. H.I.	No paralysis.
36	Aug. 20	Marvin H.*	Jordan	Dye	13	20 hrs.	99.6	110	++	++	++	++	80	—	90%	+++	10 cc. H.I.	No paralysis.
37	July 11	John M.	Syracuse	Lynech	6	20 hrs.	101	130	++	++	++	++	460	80%	20%	+++	12 cc. H.I.	Weakness back and lowers.*
38	Aug. 12	Theodore S.	E. Syracuse	Snyder	23	44 hrs.	101.6	154	++	++	++	++	90	—	—	+++	10 cc. Pn.	No paralysis.
39	Aug. 16	John A.	Eastwood	Luby	3	27 hrs.	100.4	104	++	++	++	++	260	20%	80%	+++	10 cc. H.I.	No paralysis.
40	Aug. 10	Howard B.	Syracuse	Foreman	3	21 hrs.	101.4	104	++	++	++	++	40	—	—	?	15 cc. H.I.	No paralysis.
41	Aug. 20	Peggy C.	Syracuse	Lawless	24	27 hrs.	102.0	120	++	++	++	++	180	—	90%	+++	8 cc. Pn.	No paralysis.
42	July 25	Donald D.	E. Syracuse	Bernan	11	20 hrs.	101	160	++	++	++	++	210	—	90%	+++	15 cc. Pn.	No paralysis.
43	July 21	Dorothy G.*	E. Syracuse	Snyder	6	20 hrs.	101.2	130	++	++	++	++	280	—	—	+++	15 cc. H.I.	No paralysis.
44	July 31	Hubert H.	E. Syracuse	Richardson	6	20 hrs.	102.2	132	++	++	++	++	200	10%	90%	+++	10 cc. Pn.	Slight quadriceps weakness.*
45	Aug. 17	Ralph W.	New Haven	Goewey	6	44 hrs.	103.0	130	++	++	++	++	Turbid	—	—	+++	10 cc. H.I.	No paralysis.
46	July 30	Rosetta G.	Pleasant Beach	Mahar	9	20 hrs.	103	104	++	++	++	++	410	50%	50%	+++	10 cc. H.I.	No paralysis.
47	Aug. 21	Disque D.	Cazenovia	Joy	3	48 hrs.	102	130	++	++	++	++	800	—	—	+++	15 cc. Pn.	No paralysis.
						24 hrs.	102	—	++	++	++	++	250	—	—	+++	15 cc. H.I.	No paralysis.
						42 hrs.	100.2	—	++	++	++	++	Turbid	—	—	+++	10 cc. H.I.	No paralysis.
						24 hrs.	101	140	++	++	++	++	240	—	—	+++	10 cc. H.I.	No paralysis.

Case	Sex	Age	Physician	Location	Onset	Duration	Temperature	Pulse	Respiration	Stool	Urine	Spinal Fluid	Paralysis	Remarks
1	Male	45	Ralph H.†	Syracuse	July 9	5	101.4	140	24 hrs.	48 hrs.	101.4	140	10 cc. Pn.	Paralysis of left shoulder.†
2	Male	49	Dora B.	Fayetteville	Aug. 9	14	99.4	148	24 hrs.	48 hrs.	99.4	148	6 cc. H.I.	No paralysis.
3	Male	50	Ed. W.	Syracuse	Sept. 23	14	101	130	40 hrs.	20 hrs.	101	130	20 cc. H.I.	No paralysis.
4	Male	51	Henry J.	Syracuse	Aug. 14	9	101.4	140	24 hrs.	48 hrs.	101.4	140	10 cc. H.I.	No paralysis.
5	Male	52	Thos. S.	Syracuse	July 21	3	101.2	144	24 hrs.	48 hrs.	101.2	144	15 cc. H.I.	No paralysis.
6	Male	53	Ernest J.	Fabius	Sept. 3	13	102	130	24 hrs.	48 hrs.	102	130	7 cc. Pn.	Weakness right shoulder.*
7	Male	54	Geo. C.	Syracuse	Sept. 22	5	102.4	140	26 hrs.	48 hrs.	102.4	140	10 cc. H.I.	No paralysis.
8	Male	55	Isabel W.*	Canastota	Oct. 20	6	101.4	130	26 hrs.	48 hrs.	101.4	130	10 cc. H.I.	No paralysis.
9	Male	56	Clarence N.	Syracuse	Aug. 25	6	102	132	26 hrs.	48 hrs.	102	132	10 cc. H.I.	No paralysis.
10	Male	57	Joseph G.	Syracuse	June 8	8	103	120	48 hrs.	26 hrs.	103	120	10 cc. Pn.	Weakness both quadriceps.*
11	Male	58	Evelyn I.*	Memphis	Aug. 22	9	102	130	26 hrs.	48 hrs.	102	130	15 cc. H.I.	No paralysis.
12	Male	59	Jan. K.	Syracuse	Aug. 30	14	101.5	110	28 hrs.	48 hrs.	101.5	110	20 cc. H.I.	No paralysis.
13	Male	60	Clement Z.	La Fayette	Oct. 19	32	102.3	150	28 hrs.	48 hrs.	102.3	150	15 cc. H.I.	Paralysis right shoulder.†
14	Male	61	Leo G.	New Haven	Aug. 26	6	99.8	120	28 hrs.	48 hrs.	99.8	120	15 cc. H.I.	No paralysis.
15	Male	62	Edith McC.	Syracuse	Aug. 2	19	102.4	148	28 hrs.	48 hrs.	102.4	148	8 cc. Pn.	No paralysis.
16	Male	63	James Van D.	Jordan	Sept. 6	3	102.4	130	30 hrs.	48 hrs.	102.4	130	15 cc. H.I.	Paralysis right quadriceps.*
17	Male	64	Edwin W.	Syracuse	July 31	41	100.2	130	30 hrs.	48 hrs.	100.2	130	15 cc. H.I.	Extensive paralysis 60 hrs.‡
18	Male	65	Chas. F. S.	Syracuse	July 31	24	102	112	30 hrs.	48 hrs.	102	112	10 cc. H.I.	Death 90 hours.
19	Male	66	Jennie A.*	Canastota	Sept. 26	16	101	122	30 hrs.	48 hrs.	101	122	10 cc. H.I.	No paralysis.
20	Male	67	Andrew J.‡	Syracuse	Aug. 1	5	101	140	54 hrs.	30 hrs.	101	140	10 cc. H.I.	No paralysis.
21	Male	68	Francis McK.	Syracuse	Aug. 13	5	101	140	30 hrs.	30 hrs.	101	140	10 cc. H.I.	No paralysis.
22	Male	69	Wm. H.	Syracuse	July 29	3	100.3	100	32 hrs.	30 hrs.	100.3	100	15 cc. H.I.	No paralysis.
23	Male	70	Father H.	Cazenovia	Oct. 2	6	101.4	130	32 hrs.	30 hrs.	101.4	130	10 cc. Pn.	No paralysis.
24	Male	71	David Van K.	Syracuse	Aug. 22	17	102	112	36 hrs.	36 hrs.	102	112	10 cc. H.I.	No paralysis.
25	Male	72	Arch. McD.	Syracuse	Aug. 25	6	102	112	36 hrs.	36 hrs.	102	112	10 cc. H.I.	No paralysis.
26	Male	73	Melva W.	New Haven	Aug. 10	5	102.4	124	36 hrs.	36 hrs.	102.4	124	10 cc. H.I.	No paralysis.
27	Male	74	Laure W.	Auburn	Oct. 20	12	102	118	36 hrs.	36 hrs.	102	118	10 cc. H.I.	No paralysis.
28	Male	75	Jack G.	Brewerton	Aug. 19	9	101.2	120	46 hrs.	46 hrs.	101.2	120	15 cc. H.I.	No paralysis.

POLIOMYELITIS—PREPARALYTIC STAGE.—(Continued.)

1925.

4 Cases in Syracuse—2 Deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Dura- tion.	Temp.	Pulse.	Head- ache.	Neck.	Tremor.	Apathy.	Spinal Fluid.				Serum.	Results.
													Cells.	Polys.	Lympho.	Protein.		
60	July 30	Wm. F.*	Syracuse	Novell	9	34 hrs.	101.2	124	+++	+++	+	+++	140	10%	90%	+++	10 cc. Pn.	Weakness rt. shoulder and back.*
61	Aug. 18	Austin C.*	Weedsport	St. John	12	36 hrs.	102.6	132	+++	+++	+	+++	820	60%	40%	+++	{12 cc. Pn. 15 cc. H.I.	Paralysis of left serratus.*
62	Sept. 21	Esther P.	Syracuse	Sorgues	4	55 hrs.	102	130	+++	+++	+	+	800	100%	0%	+++	6 cc. A.M. 6 cc. H.I.	No paralysis.
63	Dec. 10	Lois E.†	Cortland	Barker	3	36 hrs.	102.8	140	+++	+++	+	+	600	35%	65%	+++	12 cc. H.I.	Paralysis right shoulder.†
64	Oct. 18	Betty Jane C.	Cuyler	Padgett	3	33 hrs.	101.2	120	+++	+++	+	+++	210	90%	10%	+++	8 cc. Pn.	No paralysis.
65	Sept. 16	Grand MacD.	Syracuse	Burdick	18	60 hrs.	102	150	+++	+++	+	+++	820	20%	80%	+++	20 cc. Pn.	Extensive paralysis, death at 84 hours.‡
						65 hrs.	Paralysis of rig.		+++	+++	+	+++		74%	26%	+++		

1926.

60 Cases in Syracuse—13 Deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Dura- tion.	Temp.	Pulse.	Head- ache.	Neck.	Tremor.	Apathy.	Spinal Fluid.				Serum.	Results.
													Cells.	Polys.	Lympho.	Protein.		
96	Aug. 18	Susanne L.	Syracuse	Smith	7	10 hrs.	100.8	104	+++	+++	+	+++	240	20%	80%	+++	12 cc. H.I.	No paralysis.
97	Aug. 23	Eloise C.	Syracuse	Evans	7	10 hrs.	103	156	+++	+++	+	+++	740	50%	50%	+++	{12 cc. H.I. 10 cc. H.I.	No paralysis.
98	June 30	Cliff B.	Tully	Padgett	15	32 hrs.	101.2	100	+++	+++	+	+	825	90%	10%	+++	{10 cc. Pn. 15 cc. H.I.	No paralysis.
99	Sept. 15	Jane V.	E. Syracuse	Marsh	8	34 hrs.	101	108	+++	+++	+	+++	430	10%	10%	+++	{15 cc. Pn. 15 cc. H.I.	No paralysis.
100	Sept. 10	Herbert H.	Warners	Coe	11	13 hrs.	101	136	+++	+++	+	+++	120	—	—	+++	10 cc. H.I.	No paralysis.
101	Sept. 6	Lucille H.*	Syracuse	Maboney	12	46 hrs.	102	126	+++	+++	+	+++	560	70%	30%	+++	{13 cc. H.I. 12 cc. H.I.	No paralysis.
102	Aug. 11	Helen O'H.	Syracuse	Lawless	12	42 hrs.	101	—	+++	+++	+	+	400	90%	—	+++	{13 cc. H.I. 12 cc. H.I.	Slight weakness in left shoulder.*
103	Aug. 11	Roy W.	Falun	Gosner	8	22 hrs.	100.6	114	+++	+++	+	+	260	5%	95%	+++	15 cc. H.I.	No paralysis.
104	Aug. 4	Robert P.	Liverpool	Platner	9	30 hrs.	101.4	130	+++	+++	+	+++	820	70%	30%	+++	{12 cc. H.I. 15 cc. H.I.	No paralysis.
						30 hrs.	102.4	122	+++	+++	+	+	Cloudy	—	10%	+++	10 cc. H.I.	No paralysis.

[illegible]

CASE 95.—Grant M., aged eighteen years, was seen at sixty hours; 20 cc. of pneumococcic serum was given. Five hours later beginning paralysis of shoulder girdle was noted. Evidently a late case and hardly a frank serum failure. This boy, although distinctly ill, had tried to keep up and about during the first forty-eight hours. An adult sister died of infantile paralysis nine years before.

CASE 107.—Alfred M., aged seven years, was seen in a country district, and 10 cc. of human immune serum were given at twenty-four hours. Telephone report on the following morning was of normal temperature and great improvement, and he was not seen at this time by the writer. At seventy-two hours there was temperature of 103° F. and involvement of both uppers with subsequent respiratory death. This is a most distressing case and demonstrates the necessity for careful and frequent observation. Possibly the initial serum amount should have been larger, but by all means this boy should have had a second dose of serum.

CASE 110.—Alice S., aged three years, seen 38 miles away, received initial dose of serum at twenty-seven hours. The next day improvement reported and serum not repeated. Death on the third day from upper and respiratory paralysis. This also is a tragic demonstration of the necessity of careful watching and a proper appreciation of the importance and potential fatality in these cases. A second dose should, of course, have been given.

CASE 123.—Edward F., aged twenty-two years, was seen in a boarding house at fifty-two hours—definitely a late case. When again seen at seventy-two hours involvement of both lowers had appeared. Temperature was then down and prognosis as to no further extension was considered good. He, however, developed suddenly during the night difficulty in swallowing and died of central respiratory paralysis.

CASE 126.—Gordon R., aged twenty years, was seen at sixty-four hours, and was a very severe case. The previous clinical diagnosis was meningitis with extensive erythema suggesting purpura. This was quite evidently a late case with the appearance of paralysis at seventy-six hours.

Of these 8 deaths, 5 were vigorous young adults from sixteen to twenty-two years, and in 4 of them there was definite absence of early bed rest and appropriate care. In 3 of them, serum was given late at fifty-two, sixty-two and sixty-four hours respectively, and just before the appearance of paralysis, obviously advanced cases. In 3 others no second, or repeat, serum was given; in 2 of these, from remote districts, because of telephone reports of apparent improvement and in the third because it was not allowed by excitable and prejudiced parents. The remaining 2 cases are frank failures of serum and without alibi.

There were 25 cases that developed paralysis. Ten were mild and have cleared entirely in the course of six months. Eleven were moderately severe with residual and permanent weakness of one or more extremities. It is of interest to note that of these 25 cases with paralytic involvement only 4 were seen in the first twenty-four-hour period, and also that several might have been benefited by a second administration of serum.

There are listed 93 cases with "no paralysis." This was determined by ordinary neurologic examination directly after the subsidence of the fever and by the absence of any ordinarily detectable disability. In few of these, however, later examination by an efficient orthopedic nurse showed a "weakness of the flexor of the right big toe," or a "slight weakness of the left rectus of the abdomen," but such variations were considered as insignificant and the case considered as nonparalytic. Cases without demonstrable paralysis were allowed up and about in ten days.

Forty-six were seen in the first twenty-four hours. Of these there was one death (Case 6), and one (Case 25) with extensive paralysis. Both of these should have had repeat serum and again well illustrate the absolute necessity of close observation. Three developed mild paralyses. Forty-one recovered, without demonstrable cord involvement.

In contrast, 11 were seen after forty-eight hours. Of these, there were 3 deaths, 3 severely paralyzed, and 2 mildly paralyzed.

Six cases might be considered mild on the clinical evidence and because of the low cell counts. They are listed as follows:

- Case 3 at fourteen hours, 20 cells.
- Case 4 at fifteen hours, 50 cells.
- Case 22 at ten hours, 60 cells.
- Case 23 at ten hours, 65 cells.
- Case 29 at fifteen hours, 90 cells.
- Case 49 at twenty-four hours, 90 cells.

It must be noted that these were all early cases and might have at a later hour shown greater severity. An illustration of this is seen in Case 38, spinal fluid at twenty-four hours showed only 40 cells and serum was not given; at a second puncture, six hours later, there were then 180 cells with a much clearer clinical picture.

Case 57 serves as an illustration of the definite symptomatic picture. It was seen quite out of season on June 8, definitely diagnosed, and treated as pre-paralytic poliomyelitis. The diagnosis was at first received with doubt, because of the unusually early incidence and also the absence of other cases in the community. However, it proved to be one of the first in a subsequent series of 133 and was immediately followed by the appearance of several paralytic cases in the immediate neighborhood.

Nonspecific Serum. Of the 126 cases, 23 were given antipneumococcic serum alone and 8 were given an initial dose of pneumococcic serum and a subsequent dose of human convalescent serum. As far as can be determined from such a small number, there is no great difference in results as compared to the human immune serum. This, to the writer, is very disturbing, as it is nonspecific therapy, and hence in the minds of some might detract from the value of the entire series. No explanation is offered, except that the apparently

beneficial results may be partially due to the phagocytic action of the additional aseptic meningitis produced by this introduction of a foreign serum.

However, it is strongly urged by this observer that the human convalescent serum on the experimental evidence be used. It should also be remembered that the introduction of pneumococcus serum or other nonspecific horse serum is often attended later by severe reactions with urticaria, joint inflammation and acute kidney irritation. In this series, many severe reactions were noted in cases previously sensitized by diphtheria toxin-antitoxin. Such serum sickness does not occur with human immune serum. Therefore, pneumococcic or other horse serum is not to be recommended and was only used in a few cases when immune serum was not immediately available. Also, it has been shown by Flexner and Amos that the intraspinal introduction of horse serum in the experimental animal has seemed to increase the susceptibility of that animal to the coincidentally or subsequently introduced virus.

Serum in Paralytic Stage. The intraspinal administration of serum to the paralyzed cases is considered futile, but sometimes decision in the early paralytic stage is a difficult one. It is often demanded by the parents and the attending physician. Paralysis, well-established, cannot be very much affected by serum, but in the very early hours of paralysis with temperature remaining high, it has been the plan of the writer to examine the spinal fluid and, if the cell-count is above 200, serum is given, this on the premise that if, in the earlier meningeal stage it is of value, then it might also be still of value in neutralizing the virus yet present and possibly active in the surrounding meninges. Serum has been given in 46 such cases, many of which were severe; 18 died and no definite conclusions can be drawn in the others as to whether any benefit was obtained. It seemed occasionally as if symptoms subsided more rapidly without further extension, but, of course, there can be no proof of this and generally serum is not to be recommended in the paralytic stage.

In bulbar types puncture and intraspinal serum are contraindicated. These patients are to be left severely alone and must be kept absolutely quiet. With such quiet they sometimes "slip by" and the added disturbance by puncture and serum might well reverse the balance.

Intravenous Serum. Intravenous administration of serum as recommended by Amos, Draper and others, is difficult of attainment. It necessitates a large amount of serum which is not always available and, in the opinion of the writer, such treatment is not necessary. All the cases in this group were treated by intraspinal administration only.

Comment. It is not held that the answer of the serum problem of poliomyelitis is here presented. Undoubtedly more cases must be accumulated. However, the main argument against such a series

is in the lack of control cases and it is suggested by some that treatment should be only given to the alternate case. In answer, it is again maintained by the writer that such control is quite satisfactorily found in the paralyzed case, the case occurring in the same locality during the same period, which is undiagnosed and untreated in its pre-paralytic stage, and only recognized when paralyzed.

The argument for treatment by lumbar puncture alone cannot be satisfactorily refuted, but the author refuses to take the responsibility of demonstrating its value.

The writer is most appreciative of the fact that a very great and unusual opportunity has been afforded him. It should be noted that for every positive case seen there were many other most interesting conditions to be excluded, making for a most valuable experience. He wishes to especially express his thanks to Commissioners Thomas P. Farmer and Herman G. Weiskotten, of the city of Syracuse, in allowing him to see many of these patients, and he also wishes to express his appreciation of the valued help of Dr. Arthur N. Curtiss, who has been associated with him in this work during the past summer.

Conclusion. It is the belief of the writer that the pre-paralytic stage of poliomyelitis presents a distinct clinical entity; that diagnosis can be, and should be, made early in that stage and that human convalescent serum, administered intraspinally in this period, is of value in preventing paralytic sequelæ, and the earlier in this period, the more successful the result. It is recommended that in any community in which poliomyelitis is occurring, a "Polio" service be established with available convalescent human immune serum and a personnel of diagnosticians, preferably the laboratory man well-experienced as to lumbar punctures, and, if possible, an epidemiologist, a sanitary engineer, an entomologist and a competent administrator. Early diagnosis in the pre-paralytic stage can be made, cases isolated, appropriate treatment given and, what is most important, by such concentrated effort and study, the distinctive mode or modes of spread may be discovered. Then, and not until then, will this treacherous disease be controlled.

CERTAIN NERVOUS COMPLICATIONS FOLLOWING THE USE OF THERAPEUTIC AND PROPHYLACTIC SERA.

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FOR twenty-five years serum sickness has been a well recognized clinical entity and Boots and Homer Swift¹ but lately have gone so far as to state that most patients receiving considerable amounts of therapeutic serum develop this condition.

The picture of high fever, urticaria and leukopenia, followed by increase of white blood cells, has been for long sufficiently familiar, and, in this country, in 1923, an examination was made of patients with serum sickness in whom acute joint inflammation was a predominant symptom. Such inflamed joints were sometimes swollen and locally raised in temperature having a synovial exudate microscopically indistinguishable from that occurring in joints of patients with rheumatic fever.

The incidence of these intoxications on the skin and mesoderm has thus been recognized and understood but no mention of similar affections of the nervous system has as yet been made in American literature.

In the past two years, however, a number of such cases have come to my attention and, on investigation, it was found that in France also, since 1926 there have been reported² postseral neuritides of many peripheral varieties.

I had the opportunity a few years ago to report some cases of angioneurotic edema affecting the brain and meninges in which there occurred focal symptoms from focal dropsies; transient aphasias, transient swellings of the ocular papillæ, transient palsies and transient convulsions synchronizing with urticarial manifestations outside the nervous system. At that time I was ignorant of the nervous complications of serum sickness, some of which at least are the result of the same mechanism as in my earlier material.

Case Reports. In 1 case, to be reported in brief form there were fulminating cerebral symptoms; two had almost identical brachial plexus and circumflex nerve lesions, two others sustained unilateral paralysis of the long thoracic nerves, and 1 case of generalized polyneuritis following antityphoid inoculation will be considered.

CASE I.—T. C., aged eleven years, possessed up-to-date parents who prevailed on their medical man to protect their boy against scarlet fever by the use of prophylactic serum which two years ago had just been discovered by the Press. Four days later the boy became severely ill, was covered with urticaria and had a fever of 104° F. Headache was severe from the start; the head was retracted, the abdomen scaphoid and the significance of a constant meningeal cry was made clear by a strongly positive Kernig sign on each side.

On the third day of serum sickness, the patient became aphasic and had a partial right hemiplegia. I saw him two days later when a right homonymous hemianopia was apparent, together with total alexia and jargon aphasia, persistent headaches and the clinical picture of meningeal irritation. There was also bilateral swelling of both optic discs of great severity. Its height could not be measured for no part of the retina could be found in either eye that was not also edematous.

It was this circumstance, however, which enabled a good prognosis to be given, it being apparent that the meninges were the seat of urticarial swelling similar to that seen in the retinae and in the skin. The cerebrospinal fluid escaped under great pressure and only 14 lymphocytes could be counted per c.mm., a surprising fact in view of the severe meningeal involvement which must have been present.

Our faith in the nature of the mechanism under observation was justified by a gradual recession of symptoms in the following ten days, and four and a half weeks from the beginning of his serum sickness he was reported to me as free of signs and of complaints.

The use of atropin, adrenalin and intravenous glucose may have aided recovery.

In view of our recent Bellevue results in the reduction of intracranial tension by giving large doses of caffein this patient would have been benefited by that drug—however, that is for the future.

CASE II.—H. S., aged eighteen years, the son of one of my colleagues, was seen in February, 1927, three weeks after prophylactic inoculation against scarlet fever, which had been followed by allergic symptoms of great severity. High fever, urticaria, agonizing pains in all the large joints—which were swollen, I was informed, so that their bony form could no longer be made out. There was a numb feeling over the shoulders from the beginning. There was said to be fluid in each affected joint but this must have been hard to determine in view of the great swelling around them. The arms could not be abducted at the shoulders but little was thought of this owing to the severity of the joint pains and the fact that the swelling subsided more slowly in and around the shoulders. However, departure of the shoulder swelling was followed by shoulder atrophy; my examination showed almost total wasting of both deltoid muscles and some wasting of supra- and infrascapular muscles on each side. The right circumflex skin areas was totally without sensation, and the left almost so.

There was complete electrical reaction of degeneration in each deltoid and partial reaction of degeneration in those scapular muscles less stricken. Gradual restoration of strength has taken place during the past year; all movements can now be completed without the use of adventitious or accessory-muscle groups, and total recovery of power is in sight.

CASE III.—F. Z., aged twelve years, was given antitetanic serum on the fourth of July last year following a minor injury to a finger from fire-cracker explosion. Urticaria, joint pains, and fever followed. The shoulder joints were said to have been swollen but apparently not at all to the same degree as in my other patient. He was brought to me in October as a case of acute poliomyelitis, in that he could not raise the arms at the shoulders from the time of his illness in July. He presented a picture identical in form with my earlier patient but less complete in degree.

There was no evidence of scapular-muscle involvement, but both deltoids were wasted through not totally; there was incomplete reaction of degeneration on both sides and a definite triangle of decreased sensibility in both circumflex areas. In the past six months, there has been steady improvement in symptoms, there is no longer any sensory loss and power is in fair way to complete return.

CASE IV.—R. S., aged fifteen years, ran a spike into his foot and was given antitetanic serum on May 25, 1927, into the left arm. The arm a few days later became swollen and painful and serum sickness followed. The urticaria was extensive but was noticed to be especially severe over the right upper arm and right axilla and right side of trunk. There was no swelling of any joint, though joint pains were intense. After recovery, a deformity of the right scapula was noticed, and he was seen by me at the instance of Dr. Jagger of Flushing on June 9 last. He then had a total paralysis of the right serratus magnus muscle with completely winged scapula and weakness of abduction of the upper arm. I have not learned if any recovery has yet taken place.

CASE V.—J. A.,* aged twenty-one years, fell and sustained a superficial laceration of the scalp. He walked into the "Emergency Room" of a nearby hospital, where the wound was treated and tetanus antitoxin given into the muscles of the left arm.

He had completely dismissed the matter when on the seventh day following the trivial accident, the arm became red, swollen and painful about the site of the infection. A few hours later an erythematous rash appeared over the entire left arm and nowhere else. On the third day subsequent to the appearance of the rash, the right shoulder became painful and a trifle swollen. The pain disappeared at the end of twelve hours. Almost immediately, the left shoulder joint grew painful and continued to annoy him for seven days. The following morning (that is, the morning of the third week from the administration of serum), pain recurred in the right shoulder and persisted for forty-eight hours. There was no further increase of symptoms.

About this time he noticed a weakness of the right upper extremity. The movements of the right upper extremity were awkward. The limb seemed to be "in its own way." The muscles felt too heavy and cumbersome. The difficulty in the execution of movements progressed, and seventy-two hours after he had first become conscious of the weakness he could not raise the right arm to the horizontal position. At the same time, he remarked the winging of the right scapula. (December, 1926, he came to Bellevue Hospital.)

Past history irrelevant save for a gonococcus infection in 1924, complicated by a generalized arthritis, with total recovery.

Physical Status. The boy had an unusually well-developed powerful musculature. There was a complete paralysis of the right serratus magnus with inability to raise the right arm to a complete horizontal position; winging of the scapula was prominent with marked bulging of the intrascapular space. All other muscles were intact, including the right trapezius, upper and lower portions.

The blood Wassermann test was negative.

A radiogram of the right shoulder was negative.

CASE VI.—A. E. T., aged thirty-four years, was seen by my colleague, Dr. George Hyslop, to whose courtesy I am indebted for these notes.

In November, 1924, he was given antityphoid inoculation, the second injection being followed by a severe reaction with high fever and urticaria.

The last dose was given on December 2. The next day he awoke with numbness of the feet, a sensation which spread slowly and steadily upward to the waist. On December 7 it was felt in the ring and little fingers of both hands. He had trouble in focussing objects near him in the midline of vision. At this time there was an incomplete glove-and-stocking anesthesia, and total loss of vibration sense in the legs. The grasps were weak and awkward. Tingling in the hands and feet was painful, and he felt desperately tired. The deep reflexes persisted but were much reduced. For a month the abdominal reflexes could not be obtained.

His symptoms remained for about eight weeks in all, during which time gradual improvement took place.

There are, of course, two possible processes, either of which might produce these conditions. The toxicity of the serum or the urticarial edema of the perineural tissue. Probably both are factors, but I believe the latter mechanism was chiefly responsible for the symptoms of my first cerebral case, and also in the cases of paralysis of

* History kindly procured by my Bellevue Hospital physician, Dr. Aaron Bell.

single long nerves. Here there was clearly palsy by compression and not palsy by destruction of nervous parenchyma.

The site of paralysis coincided with the site of greater incidence of edema; and there was entire absence of nerve involvement other than in the severely affected nerve.

The last case in which polyneuritis followed urticaria consequent to antityphoid inoculation must have been largely toxic in origin, and so in a different causal category.

Conclusion. 1. In view of the occurrences here reported some of great gravity—it would seem wise, before giving serum, to use intravenous injection of sodium carbonate.

2. Immunizing methods which will diminish serum sickness must be devised. In this connection, one remembers how very rare were such conditions during the World War when antitetanic serum was given in hundreds of thousands of doses.

3. When all has been said, however, these are rare accidents, and but a small price to pay for the inestimable benefits obtained by serum therapy in general.

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SEX, AGE AND SEASONAL DISTRIBUTION OF TETANY IN THE ORPHANAGES IN PEKING

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IN our metabolic studies^{1,2} of the type of tetany that occurs in the orphanages in Peking, it has been shown that this condition cannot be accounted for solely by the low-calcium intake in the diet, and that a deficiency in vitamin D as contained in cod-liver oil or lack of available ultraviolet rays in the sunlight plays an even greater part in bringing about a condition of neuromuscular hyperirritability. Mention was also made of the great prevalence of tetany in these institutions, but exact data were not available. It is the purpose of the present communication to report on the incidence of tetany in two of the orphanages in Peking with respect to sex, age and season.

One of the orphanages studied is situated outside the city, the other inside the city. The bulk of the material was obtained from the institution outside of the city, while the other orphanage supplied data for only 80 girls. As the two orphanages are under the same management and environmental conditions, the data obtained from them were treated together. The boys and girls in the two orphan-

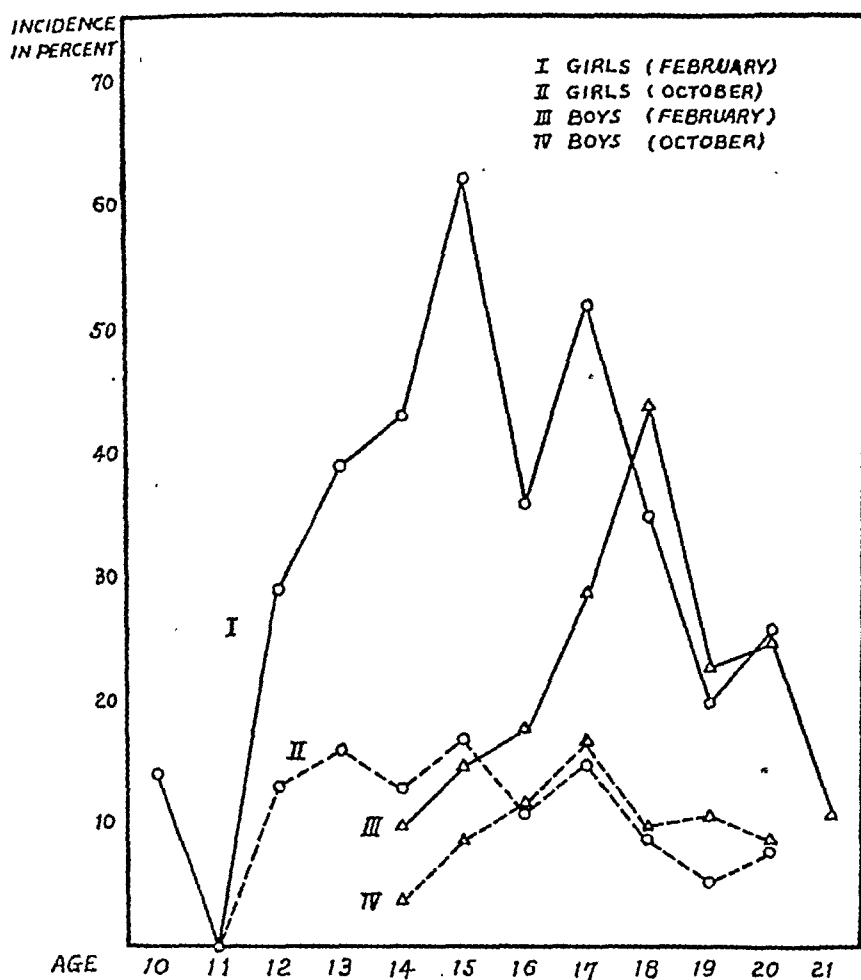


Figure showing sex, age and seasonal variations in the incident of tetany in two orphanages in Peking.

ages were examined in February, 1927, and again in October of the same year. In each case, a history of past and present attacks of spasm of hands and feet was taken, and an attempt was made to elicit Chvostek's sign (facial phenomenon) and Trousseau's sign. Greater emphasis is placed on Chvostek's sign in the diagnosis of tetany, as this sign is found sufficiently reliable and very convenient, especially in dealing with a large number of subjects.

Results. *Sex.* Table I represents the results of examinations made in February, 1927, the late winter season of the year in this

region. The incidence of tetany in females is distinctly higher than that in males. Among the 337 girls examined, 118 (or 35 per cent) showed evidence of various grades of increased neuromuscular irritability, from a positive Chvostek's sign alone to active symptomatic manifestations. However, of the 351 boys examined, only 80 (or 22.8 per cent) exhibited the facial phenomenon and no case of active tetany was observed.

TABLE I.—INCIDENCE OF TETANY ACCORDING TO AGE AND SEX IN FEBRUARY, 1927.

Age.	Male.			Female.		
	Total number examined.	Number showing evidence of tetany.	Percentage affected.	Total number examined.	Number showing evidence of tetany.	Percentage affected.
5	1	0	0	1	0	0
6	1	0	0
7	5	0	0
8	3	0	0	3	0	0
9	4	0	0	6	0	0
10	7	0	0	7	1	14
11	4	0	0	8	0	0
12	8	0	0	7	2	29
13	4	0	0	18	7	39
14	20	2	10	21	9	43
15	27	4	15	29	18	62
16	50	9	18	39	14	36
17	69	20	29	56	20	52
18	57	25	44	63	22	35
19	52	12	23	45	9	20
20	28	7	25	26	7	26
21	9	1	11	4	0	0
22	1	0	0	2	0	0
23	2	0	0
24	1	0	0
All ages	351	80	22.8	337	118	35.0

Age. The age of the subjects examined varied from four to twenty-three years. No cases of tetany were found among the boys before the age of fourteen years. From then on, the incidence of tetany increased with age up to eighteen years when a maximum was reached. After eighteen years, the rate of tetany gradually declined, and after twenty-one years no case was observed, although this age group was small. The onset of tetany in girls was earlier. It began to make its appearance at the age of ten years, and a maximum incidence of 62 per cent was obtained at the age of fifteen years. No cases of tetany were recorded among the girls after the age of twenty years.

Season. If the results obtained in October, the late summer season of the year (Table II), are compared with those in February

(Table I), the reduction in the rate of tetany in the summer is striking. There were only 9.8 per cent of the boys and 10.9 per cent of the girls in whom the facial phenomenon was demonstrable, as contrasted to the corresponding figures of 22.8 and 35.0 per cent obtained in the winter. Not a single case of active tetany occurred either in the male or female group in the summer. The age distribution of tetany was similar in the two seasons. The sex difference in the incidence of tetany, marked in the winter, did not appear to be present in the summer.

TABLE II.—INCIDENCE OF TETANY ACCORDING TO AGE AND SEX IN OCTOBER, 1927.

Age.	Male.			Female.		
	Total number examined.	Number showing evidence of tetany.	Percentage affected.	Total number examined.	Number showing evidence of tetany.	Percentage affected.
4	1	0	0	3	0	0
5	2	0	0	4	0	0
6	3	0	0	3	0	0
7	2	0	0
8	5	0	0	5	0	0
9	3	0	0	8	0	0
10	9	0	0	7	1	14
11	2	0	0	5	0	0
12	8	0	0	15	2	13
13	5	0	0	31	5	16
14	25	1	4	35	5	14
15	34	3	9	35	6	17
16	60	7	12	57	6	11
17	79	13	17	62	9	15
18	75	7	9	55	5	9
19	55	6	11	36	2	6
20	31	3	9	24	2	8
21	5	0	0	5	0	0
22	1	0	0	1	0	0
23	2	0	0
All ages	405	40	9.8	393	43	10.9

Discussion. The great prevalence of tetany in the orphanages concerned suggests the operation of some factor or factors that are related to their diet. Hammond and Hsia³ have carefully investigated their diet which consists chiefly of millet, wheat and corn meal. It is the same throughout the year, there being no change except occasional substitution of vegetables in season. The fat intake is very low, the protein intake moderately low, and the carbohydrate intake correspondingly high. Calculation from the dietary lists shows that the daily average intake of calcium is approximately 0.004 gm., and that of phosphorus 0.012 gm. per kg. of body weight. Both the calcium and phosphorus intake are far below the minimum

requirements according to the criteria of Shohl and Sato⁴ and Ehrström.⁵ Undoubtedly, the deficient intake of calcium and phosphorus plays a part in the etiology of tetany, but it does not explain the marked seasonal variation, as the diet remains approximately constant throughout the year. As the incidence of tetany varies inversely with the intensity of the ultraviolet rays of the solar spectrum, a more plausible explanation would be that the ultraviolet rays, being more intense in the summer, are sufficient to make up whatever deficiency there is and thereby decrease the incidence of tetany, but that they become insufficient in the winter, thereby causing a great increase in the rate of tetany. This deficiency in the winter is enhanced by longer hours indoors on account of cold weather.

The relationship between ultraviolet rays and tetany is further established by the therapeutic results achieved with the use of ultraviolet rays in this type of case.²

The occurrence of tetany solely in the age groups between fourteen and twenty-one years in the male and between ten and twenty years in the female suggests an association, perhaps more than coincidental between puberty and a tendency to increased neuromuscular irritability. The influence of puberty, if there be any, seems to be even greater on the female than on the male, as the incidence of tetany is higher among the girls than among the boys. Mirvish and Bosman,⁶ working on the influence of the internal secretion of the ovary on calcium metabolism, have demonstrated that alcoholic extracts of ovary, liquor folliculi, and corpus luteum reduce the blood calcium in rabbits from 15 to 12 mg. per 100 cc. Similar effects have been observed in human subjects.⁷ In the light of this work, may the onset of ovarian function during puberty through association with a lowering of blood calcium offer an explanation of the relatively great incidence of tetany in girls during the age period of thirteen to twenty years, when ovarian activity commences?

Summary. A large group of boys and girls in two orphanages in Peking was examined for evidence of tetany in February and October of 1927. Tetany is more prevalent among girls than boys. It affects the male during the age period of fourteen to twenty-one years, and the female during the age period of ten to twenty years. The incidence is much higher in the winter than in the summer.

Acknowledgment is made to Dr. Chu Han-ying of the Hsiang Shan Orphanage for her kind assistance in this work.

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CARBON DIOXID IN THE TREATMENT OF HYPOSTATIC PULMONARY CONGESTION.

A PRELIMINARY REPORT.

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RECENT developments have emphasized the importance of a more exact consideration of the physiology of respiration with reference to its clinical applications. Particularly has the subject of respiratory stimulation attracted attention. From the earlier neurogenic theory of the respiratory regulation the pendulum has swung to the chemical theory and carbon dioxid is held to be the respiratory hormone. Haldane, in a masterly review of the subject,¹ concluded that "under normal conditions, excluding heavy work, the breathing in man is on an average regulated by the alveolar CO₂ pressure; and a very slight increase or diminution in the CO₂ pressure suffices to cause a very great increase or diminution in breathing." Furthermore, it was established by Hough² that the primary response to an increased carbon dioxid content of the respired air is in the depth of inspiration. Twenty-three of 25 subjects showed an early response in this direction and the increase of depth was most marked when attendant upon a decrease in the respiratory rate.

In the present relation the coincident action of carbon dioxid on the cardiovascular system must be given consideration. Concurrent vasomotor and respiratory stimulation were remarked by Kaya and Starling³ in spinal animals breathing a mixture of 5 per cent carbon dioxid with an excess of oxygen. An elevation of blood pressure, therefore, resulted from this procedure. They concluded that a "moderate increase of carbon dioxid in the blood has no injurious effect on the heart and may possibly, in fact,

improve the functional capacity of the heart muscle." Further studies by Jerusalem and Starling⁴ revealed a relaxation of the heart if the carbon dioxide tension of the blood circulating in the coronary system were increased. Of great clinical significance was their determination of a reduced ventricular output at high percentages (12 to 20 per cent of an atmosphere) of carbon dioxide in the coronary circuit. On the other hand, "with moderate tensions of CO₂ (2 to 8 per cent of an atmosphere) the ventricular output increased with increase in CO₂ tensions."

The clinical applications of these facts have been varied. Henderson and Haggard⁵ utilized carbon dioxide to combat the respiratory depression of carbon monoxide poisoning. Of the efficacy of this measure there is ample and accumulating evidence. Levi⁶ and Cotton⁷ had earlier suggested the availability of carbon dioxide in combating surgical shock. Cotton especially stressed the clinical indications of a stimulation of peristalsis by carbon dioxide. Henderson, Haggard and Coburn⁸ advocated the use of carbon dioxide in the de-etherization of surgical patients. The following important results were claimed for this treatment: (1) Overventilation washes the anesthetic out of the blood, thereby shortening the duration of the anesthesia; (2) the circulation is stimulated by the hastened venous return from increased respiratory movements; (3) decreased nausea, vomiting and thirst and restoration of intestinal tone are noted. In 1925 Head⁹ advocated the use of carbon dioxide inhalations prophylactically and therapeutically in the management of postoperative massive collapse. Scott and Cutler¹⁰ have recently offered substantial evidence for the value of this procedure. Henderson¹¹ has advocated inhalation of carbon dioxide in the asphyxia of the newborn.

Yet another indication for its use may be found in the hypostatic pulmonary congestion occurring in postoperative surgical cases and in aged and debilitated individuals compelled for one reason or other to maintain a fixed recumbent position. A clearer understanding of the problem may be gained by a consideration of the contribution of normal respiration to the circulation. The inspiratory act induces an appreciable increase in the intrapleural negative pressure, which in turn exerts an active suction on the great venous trunks. The flow of the blood toward the right heart is thus greatly accelerated. According to Macleod,¹² 8 per cent of the total blood is found in the lungs at the height of inspiration as compared with 5 to 7 per cent in expiration. Hence the movement of blood dependent upon respiration is considerable. If the right heart be adequate, the pulmonary circulation is augmented and in turn the output into the systemic circulation rises late in inspiration and continues at a higher level until the expiratory fall of intrapleural negative pressure effects a decrease in the venous inflow. It will be recalled that, while expiration interrupts the flow of blood into the thorax,

it favors the movement of the blood from the lungs into the left heart. Macleod¹² concluded that "it is obvious that increased depth and frequency of the respiratory movements will accelerate the bloodflow and tend to raise the blood pressure." On the other hand, Henderson¹³ demonstrated a sharp fall in blood pressure on voluntary hyperpnea. In experimental animals under artificial respiration, succeeding a period of elevated arterial blood pressure, there was observed a shocklike state due to carbon dioxid want. Henderson and Harvey¹⁴ later adduced evidence in proof of the venopressor action of carbon dioxid and stated that acapnia produces circulatory failure by decreasing the venous return to the heart. The available experimental data indicate that increased respiratory rate and depth increase the pulmonary flow and in turn the general circulation; arterial blood pressure thereupon rises. Lastly, a certain tension of carbon dioxid in the blood is optimal for the proper functioning of respiration and circulation.

Hypostatic pulmonary congestion constitutes an important surgical problem in postoperative cases in general, but more especially in the aged and debilitated, as has been previously stated. An important and characteristic group of such serious risks is seen in fracture of the neck of the femur. It is an "old-age fracture." Such a patient is confronted first with the danger of a bronchopneumonia, which if it occurs is almost always fatal, and second the possibility of non-union, the incidence of which is greater than in any other fracture. Hence, the dismay of the physician on being called to treat such a patient is not difficult to explain. It probably lends force to the truth of the statement that "in the interest of their patients they let them die."

The factors of decreased ventilation are accentuated by the fixed recumbency enforced by the plaster of Paris and the debility common to the subject. If the influence of the respiratory movements on the circulation be admitted, clearly any reduction in their rate or depth will impair their contribution to the circulatory efficiency. Passive congestion will occur in the lungs in positions determined by hydrostatic pressure. Dependent congestion may be anticipated or stagnation may occur in local areas of peculiar immobility. Deficient myocardial tone would obviously contribute to the vicious cycle.

Whitman,¹⁵ who advanced the abduction method of treatment now in use, also made provision for the prevention of the bronchopneumonia which so often follows enforced recumbency in the aged. It consists of turning the patient first on the abdomen then on the back. This is of the greatest value in the prevention of a hypostatic congestion of the lungs and should be a routine procedure. It is at best, however, a gravity method, and it is for this reason that the present plan is offered, not to supplant, but rather to act in conjunction with the former method.

The therapeutic indication is for an active respiratory stimulant, and carbon dioxid (with oxygen) furnishes an ideal agent for this purpose. If used as advocated by Henderson and Haggard⁵ in asphyxia the concentration of carbon dioxid (5 per cent) will be adequate for respiratory and vasomotor stimulation and yet well within the limits of safety as given by Jerusalem and Starling.⁴ Furthermore, the exhibition of the gas itself as the respiratory stimulant will obviate the danger of washing carbon dioxid out of the blood. The deeper respirations induced by the inhalation of carbon dioxid will improve the pulmonary circulation (and in turn the arterial blood pressure will be elevated). The improved pulmonary circulation from increased pulmonary motility may prevent or correct hypostatic congestion of the lungs.

Since 1925 inhalations of 5 per cent carbon dioxid in 95 per cent oxygen have been given to a series of 10 patients with fractures of the neck of the femur admitted to the Orthopedic Service at the State of Wisconsin General Hospital. It should be stated that this group constituted the poorest possible physical risk. All, in whom the gas was used, were very old. Many of them had been transported to the hospital from a distance. As a rule, the fractures had not been reduced as soon as they might have been. In one case an interval of two weeks elapsed between the reception of the fracture and its reduction. Two of the patients died. One, a woman, aged eighty-three years, was received at the hospital the day of the fracture and died four days later, in spite of treatment. The autopsy showed bronchopneumonia. The second fatal case, a woman, aged seventy-six years, had received her fracture fourteen days previous to admission. She had a fever on admission which continued until the time of her death four days later. It is probable that in this case it was unwise to give carbon dioxid because pneumonia was suspected at the time of admission. In 6 of the total of 10 cases hypostatic congestion was established on the basis of decreased vibratory phenomena, suppressed breath sounds and showers of fine crackling râles in the dependent portion of the lungs. As a rule, the physical findings were unaccompanied by serious evidence of respiratory embarrassment, although in 4 instances there was definite dyspnea and cyanosis. In 2 cases the temperature curve suggested an infectious background for the respiratory symptoms and signs. There was dramatic relief of the respiratory distress and cyanosis with coincident clearing of the physical signs of hypostatic pulmonary congestion in 2 of the cases. This group of patients is contrasted with another of 10 cases of fracture of the femur in which carbon dioxid was not used, because it was considered unnecessary. Four of this control group died; 1, very suddenly of pulmonary embolus seven days after admission, 2 of the remaining 3 from bronchopneumonia and the fourth case from late pulmonary embolism.

No rule can be formulated for the dosage of carbon dioxide under these circumstances. Strict attention must be paid to the respiratory response and to the comfort of the patient. As soon as the patient begins to show signs of discomfort or fatigue, the administration of the gas is stopped. Ordinarily a patient will show some distress after two or three minutes. In such cases the mask should be removed and the respiratory rate and depth be permitted to subside. The interval between the inhalations can only be determined by the judgment of the operator. In some cases it is given every hour, in others every three hours, depending on the condition of the patient. Since hypostatic pneumonia is usually a complication of the first week, the advised use of carbon dioxide is especially important during this period. The method should be considered prophylactic rather than curative. The suspicion or actual existence of a pneumonia is an absolute contraindication to its exhibition.

Conclusions. 1. Hypostatic pulmonary congestion may occur in the aged and debilitated as the result of depressed respiratory motility.

2. In such cases as fractures of the femur an apparent relief of early hypostatic pulmonary congestion has resulted from the intermittent inhalation of carbon dioxide.

3. The rate and duration of the administration of carbon dioxide may be controlled by the respiratory response and the comfort of the patient.

4. Differentiation of pulmonary stasis resulting from respiratory depression and that dependent upon right-heart failure must be clearly made, since the use of carbon dioxide inhalations might be strongly contraindicated in the latter circumstance.

5. Overventilation may disseminate an infection from the bronchi or in the alveoli. Hence carbon dioxide inhalations are contraindicated in bronchitis or pneumonia and should also be avoided if such be suspected.

6. On physiologic grounds, a prophylactic value attaches to the use of this measure in all surgical cases meeting the discussed indications, but numbers of cases will be required to establish its value in this relation.

NOTE.—In *Current Researches in Anesthesia and Analgesia*, 1928, 7, 187, Sise, Mason and Bogan have suggested the use of carbon dioxide inhalations in the prophylaxis of postoperative pneumonia. Their observations of the improved mobility of the diaphragm as viewed under the fluoroscope are noteworthy. Their results were either equivocal or unfavorable but further studies were advocated before drawing any definite conclusions.

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THE TOXIC PSYCHOSES: AN ANALYSIS OF ONE HUNDRED CASES.

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IN view of the fact that many cases of the toxic psychoses are accompanied by uncertainty as to diagnosis, we thought that it would be of considerable value, if we analyzed the records of 100 such cases that have come to our attention, directly or indirectly, in the psychopathic ward of a large general hospital. Toxic mental states are common, and a busy general practitioner observes them daily. We took for study all cases with a diagnosis of toxic psychosis which entered the hospital between 1917 and 1925 except: (a) Organic diseases of the brain; (b) alcoholics; (c) seniles; (d) many cases of influenzal psychoses; (e) many cases of puerperal psychoses. We have omitted many of the latter two types because they were so numerous that the whole series might have been predominated by them had no discrimination been shown; furthermore, we endeavored to include only those of the puerperal cases which were on a toxic basis, thus excluding those whose mental ill health was due to dementia precox and manic depressive insanity. It is well known that a psychosis peculiar to the puerperium does not occur. As far as richness of material is concerned a similar state of affairs exists, even in this day and generation, in regard to alcoholics. For various reasons the seniles were not considered.

The ages of the patients varied from sixteen to fifty-eight years with the exception of 3, whose ages were thirteen, fourteen and sixty-eight; the average age was thirty-four, that of the females was thirty-one and of the males thirty-nine years. Sixty-six were

females and 34 were males; the number of females exclusive of those suffering from psychoses occurring during the puerperium was 44. The predominance of females is in keeping with the well-known observation that the nervous system in woman is more vulnerable to poisons. As to race, 53 were native born, 31 white and 22 colored; the remainder was made up of a variety of races. The occupation of the individual seemed to have no bearing on the development of the psychosis with the exception of three lead-workers, whose mental ill health was probably traceable to their occupation. The length of time in the hospital was from two to eighty-two days with an average of twenty days. There was a history of previous mental disturbances in 8 cases, 6 of which had had but one previous mental upset and 2 had had two attacks. Three of the 8 were puerperal and in 2 of them the attack occurred following the birth of the first child. Of the puerperal cases, 11 were undoubtedly primipara, with the possible addition of 4 more. One was Para II, one Para III, one Para IV, one Para V and one Para VI.

ETIOLOGIC FACTORS AND RESULTS.

Etiologic factors.	Total No. of cases.	Cured.	Im- proved.	Unim- proved.	Died.
Puerperal	22	8	6	1	7
Influenza	15	12	3
Pulmonary tuberculosis	7	2	5
Postoperative	4	2	..	1	1
Nephritis	4	2	2
Veronal	1	1			
Acetanilid	2	1	1		
Cocaine	1	1			
Lead	3	3			
Hyperthyroidism	2	1	1
Bronchopneumonia	2	2			
Chorea (Sydenham's)	3	2	1
Bronchitis	1	1
Bronchiectasis	1	1
Pyonephrosis	1	1
Tetanus	1	1			
Infection of arm	1	1			
Typhoid	1	1			
Mumps	1	1			
Pellagra	1	1
Pleurisy	1	1			
Pelvic abscess	1	1
Carcinoma	3	3
Mitral stenosis	1	1			
Myocardial degeneration	1	1
Septicemia	1	1			
Unknown	18	9	6	2	1

Character of the Psychoses. In analyzing the mental symptoms from which these patients suffered it is easy to understand why so

many of them were at first thought to be examples of dementia precox; it is due to the great frequency of auditory and visual hallucinations occurring in conjunction with delusions of persecution, mental symptoms, which if they occur in young adults, are always suggestive of schizophrenia. In addition, however, 21 of the patients were disoriented as to time and place and were agitated, violent and talkative. Forty-seven had a combination of auditory and visual hallucinations as the chief mental symptoms and 32 had visual and auditory hallucinations and delusions of persecution. Confusion was a common symptom and occurred at least twenty-one times. Depression, homicidal and suicidal tendencies, olfactory hallucinations, delusions of grandeur, in fact the whole run of mental symptoms were present in some.

Duration. The shortest duration with recovery was one day; the longest was one and a half years; the average duration in the cases with recovery was six weeks. Thirty patients had had fever in the course of the illness, although a great many more, such as those occurring after influenza, had had an elevation of temperature during the acute illness.

Heredity. While the records were frequently incomplete about this important phase of the history, in only 4 was there a distinct history of mental disease or epilepsy in the family. This is almost too good to be true, because the histories of 100 supposedly normal people would show a larger number of mental diseases in their respective families than does our series.

Laboratory Findings. The urine was examined in 92 of the cases and showed albumin in 21 and casts in 11. A blood Wassermann was taken in 84 and was positive in 10, but in our opinion none of these cases were general paresis, although syphilis may have played a rôle in the production of the mental aberration. Blood chemistry studies were carried out in 40 of the group and showed practically no deviation from the normal, except that 4 had a blood-sugar estimation from 150 to 180. The spinal fluid was studied in 35 cases, 3 of which had positive Wassermans with the cholesterinized antigen alone and none had a positive reaction with the Noguchi antigen. The colloidal-gold curve was negative in all in which the fluid was examined with the exception of 2, in both of which it was of the so-called syphilitic type and in both of these the Wassermann was negative. Complete blood counts were recorded in only 8, 7 of which had a leukocytosis ranging from 14 to 40 thousand; 1 case showed basophilic degeneration.

Outcome. Fifty-three were discharged as recovered; 13 improved; 4 unimproved; 30 died. The etiologic factors in the 4 unimproved cases, were exophthalmic goiter, postoperative, pregnancy and the fourth, unknown. The largest number of deaths, (7) occurred among the puerperal psychoses. Five deaths were due to tuberculosis and 3 to carcinoma. Autopsies were performed on 7

of the subjects, but in only 2 of these was the brain examined; in 1 case the brain presented a cerebral edema and in the other showed marked congestion and neuronophagia.

Follow-up Investigation. Follow-up visits were made in 53 instances, in 10 of which, however, no information about the patients could be obtained, so that completed reports number 43.

The last patient included in our series was discharged from the hospital in December, 1925, so that all cases have been disposed of practically one year or more, and a large percentage returned home a number of years ago. Thirty-six of the patients have remained mentally well since their stay in the hospital and have resumed their former occupations. One of the 36, however, died four years after discharge, but his psychic health was unimpaired until the time of his death. He was a printer, and the etiologic factor was probably lead; he dropped dead while working at his machine, so that his death was probably of cardiac origin.

Five of the patients whom we investigated since their return home had second attacks. The first of this group was an Italian male who had a postinfluenzal psychosis and was discharged cured, although it is proper to say that he could not speak English and his supposed cure may have been due to the fact that he became quiet, whereas formerly he had been disturbed. In any event, after his discharge from the hospital he became worse and committed suicide six months later. Another patient, a woman, aged twenty-four years, had a recurrence of her psychosis from which she also recovered and at the present time is normal mentally. This patient has pulmonary tuberculosis. The third was a male, aged fifty-five years, who was discharged as improved but never entirely regained his health. He was discharged against advice and died six months afterward. He had chronic bronchitis and asthma. The fourth case was a white woman, aged fifty years, whose first attack of mental illness lasted only eleven days and the etiologic factor was thought to be mitral stenosis. She had a second attack during which she was committed to the mental department at Byberry and subsequently was paroled from that institution. The fifth patient who had a recurrence was a white woman, aged twenty-five years, who became mentally ill six weeks after delivery and recovered rather quickly. Subsequently, she was committed to the Pennsylvania Hospital for Mental Diseases and again recovered her mental health. It is worthy of note that this woman later died of pulmonary tuberculosis; the frequent occurrence of intrathoracic disease is significant. Two of the cases about which good follow-up records were obtained remained broken mentally. Of the 8 patients who had had previous mental upsets only 4 could be located. Three of them have remained mentally well until the present time; the fourth is a woman who has pulmonary tuberculosis and she has had a third attack.

Discussion. As mentioned before, we have omitted alcoholics and seniles and many cases of influenzal and puerperal psychoses. Some conditions which frequently are complicated by mental symptoms are missing from our list of etiologic factors, such, for example, as primary anemia and diabetes mellitus; their absence is probably due to the fact that the records of those patients are usually not filed under the heading "toxic psychosis." Furthermore, a great many patients who have mild mental symptoms which occur in the course of kidney, liver, cardiac and pulmonary disease have not been included, as they are not customarily transferred to the psychopathic department as long as they do not upset the ward to which they have been assigned. We are fully aware of the frequency with which mental symptoms occur in all of the foregoing conditions.

The history of the onset in a great many of our 100 cases was sudden; quite a few of the records read "Patient picked up by the police and brought to the hospital." The abruptness of onset should be enough to put the diagnostician on his guard as to the possibility of a toxic psychosis, especially if paresis and other forms of organic cerebral disease can be excluded. A toxic psychosis may simulate very closely dementia precox and it is here that the differential diagnosis must be very carefully considered. The family histories in instances of patients who have dementia precox usually reveal nervous or mental disease in some form, whereas, as we have mentioned above, very few of our cases had bad mental heredity. Hallucinations and delusions of persecution are common to both forms of mental disease. The patient with a toxic psychosis is usually more talkative, more excitable, and the symptoms in general are more bizarre than those of dementia precox. Many individuals, psychotic from a toxemia, early become partly disoriented, a symptom which does not so quickly occur in an adolescent psychosis. To differentiate the two conditions it becomes evident, therefore, that a most careful and exhaustive physical examination is necessary, especially if a fever or signs of toxemia are present. The physician to whose care the treatment of any group of patients with mental symptoms falls should be fully aware of the possibilities, and if not equipped himself to ferret out the cause, he should call into consultation an internist. Every psychiatrist, however, should have a good fundamental training in internal medicine, without which he is frequently lost in a sea of uncertainty. It is needless to say that psychoanalysis will not aid in the diagnosis of the group.

The toxic factor in the psychoses is not confined to the group of cases which we have discussed, but is a very important one in all mental diseases, especially dementia precox, although the exact nature of the toxemia is usually elusive.

The prognosis, generally speaking, in an ordinary toxic case is good and the list of recoveries is large. The number of deaths, 30 in our

series, attests to the severity of the underlying toxic factor, some of which render the prognosis hopeless from the start.

Summary. The analysis of the cases admitted to the observation ward of the psychiatric service of the Philadelphia General Hospital reveals that many of these patients suffer from various forms of toxemias and physical defects which give rise to psychiatric reactions of a toxic nature. The frequency of such reactions makes it imperative that each mental case be studied most thoroughly from the history and physical standpoint to determine if such factors exist. The range of etiologic factors is wide.

REVIEWS.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY (Volume III). By D. THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London and R. THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 316; 57 illustrative plates. Baltimore: The Williams & Wilkins Company, 1927.

VOLUME III of these Annals is entirely devoted to the Streptococcus Group. It is an attempt to differentiate graphically and otherwise between the large numbers of varieties of streptococci. It is an effort also to compile a reference work of value to the research worker, an attempt to present to him a more or less organized mass of information on the work which has been done on the subject up to the present time.

There is presented a full account of the bacteriologic researches describing the streptococci—as to their morphology, cultivation, staining, cultural characteristics on various media, technique for isolation, biochemical reactions, soluble products, virulence, immunity reactions, filtrates, mutations and pleomorphism. There is also included a historic review of streptococci described in the past, various classifications including that by the use of Crowe's differential medium, and a complete bibliography. A most valuable aid to the research worker is presented in 57 full-page illustrative plates which contain 385 very exceptional photomicrographs. Five of these plates are in color.

The Volume is to be recommended to the research worker; it will undoubtedly help him to see clearly the problem that is before him and enable him better to avoid the mistakes which have been made in the past.

W. K.

IDIOSYNCRASIES. By SIR HUMPHREY ROLLESTON, BART., K.C.B., F.R.C.P. Pp. 119. London: Kegan Paul, Trench, Trubner & Co., Ltd., Broadway House, Carter Lane, E. C., 1927. Price, 2/6.

THIS handy little volume, No. 8 in the Medical Series of Psyche Miniatures, is an interesting disquisition by an able author upon

the current opinions on the subject of idiosyncrasies, "the abnormal reactions in an otherwise normal person, which may be either, on the one hand, greatly exaggerated or, on the other hand, greatly diminished," as finding their expression clinically in the diseases in which hypersensitiveness is a proven or a suspected factor.

R. K.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY (VOL. IV, PART I). By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.PH. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London; and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 250; 49 photographs. Baltimore: The Williams & Wilkins Company, 1928.

VOLUME IV of these *Annals*, devoted to the pathogenic streptococci, is presented in two parts. Each part appears in a separate volume and includes four monographs. The streptococci are examined in relation to the different diseases with which they can be identified, and a separate monograph compiled on each disease. Part I includes the four completed monographs:

1. The Rôle of the Streptococci in Rheumatic Fever.
2. The Rôle of the Streptococci in Chorea.
3. The Rôle of the Streptococci in Erythema Nodosum.
4. The Rôle of the Streptococci in Carditis.

The streptococci isolated from cases of rheumatic fever by Small, Birkhaug, Barlow and others are presented to the research worker in 49 remarkably clear photographs, illustrating certain of their cultural characteristics and morphology.

This volume includes only the first four of the monographs dealing with pathogenic streptococci, a subject which will be completed in the further volumes now in preparation, to wit: Vol. IV (Part II), Vol. V, Vol. VI and Vol. VII. This volume is, therefore, especially important as a unit in the proposed comprehensive study of pathogenic streptococci which will undoubtedly aid materially in identifying the great majority of the many varieties of streptococci.

W. K.

CONVALESCENCE. HISTORICAL AND PRACTICAL. By JOHN BRYANT, M.D. Pp. 269; 94 illustrations. New York: The Sturgis Fund of the Burke Foundation, 1927.

THIS work contains a miscellaneous collection of chapters which deal primarily with the subject of convalescence. The book, however, is not in any sense a textbook or handbook on the subject. The first fifty pages are devoted to a chronologic review of the subject and then follow chapters on the Burke Relief Foundation,

Cleveland Hospital and Health Survey and Houses of Rest in Russia. Part II is chiefly concerned with the convalescent work carried on in the United States Army and Part III is a progress report from 1920-1927. It is not a book for the student of medicine or the practitioner, unless he wishes specialized information concerning convalescence.

O. P.

TOTAL X FOTOS. By DR. DENIS MULDER, Dir. Med. Rad. Instit. Pp. 57; 38 illustrations. Bandoeng: G. C. T. Van Dorp & Co., 1927. Price, \$1.80.

In this short monograph, the author has attempted to outline advantages for making radiograms of a part or the entire body at 10 meters. In most roentgen laboratories, films are readily made at a target film distance of 2 meters. At that distance the amount of distortion is approximately 4 per cent. For all practical medical purposes, the 2 meter seems adequate. Increasing the target film distance to 10 meters in the examination of patients is not practical, because of the time, of the exposure, movement of patient, and so forth. The value of roentgenographs of paintings, statuettes, wood carvings, and so forth, are illustrated and discussed.

E. P.

BLOOD AND URINE CHEMISTRY. By R. B. H. GRADWOHL, Director of the Gradwohl Laboratories and IDA E. GRADWOHL, Instructor in the Gradwohl School of Laboratory Technic. Pp. 542; 117 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, \$10.00.

APPROXIMATELY half of the book is devoted to a description of those methods for chemical analysis of blood and urine that are used in the laboratory of a general hospital. The latter part of the book is given over to the interpretation and application of chemical methods to disease, particularly nephritis, diabetes and gout. The final chapter is devoted to basal metabolism.

The author quotes extensively from the literature, in fact a considerable part of the book is transcribed from other authors.

The book may be useful in a hospital laboratory but one would hardly consult it for authoritative statements because apparently the author, in his conservatism, has failed to give more recent methods and to state the more recent views on the subjects that he treats. The text is too long for a simple technique book and not sufficiently judicial for a treatise.

L. J.

EXERCITATIO ANATOMICA DE MOTU CORDIS ET SANGUINIS IN ANIMALIBUS. By WILLIAM HARVEY, M.D. Tercentennial Edition. With an English Translation and Annotations by CHAUNCEY D. LEAKE, Professor of Pharmacology, University of California. Pp. 154; 10 illustrations. Springfield, Illinois: Charles C. Thomas, 1928. Price, \$3.50.

AMONG the more permanent reminders of the Harvey Tercentenary—an anniversary worthily celebrated in many countries and in many ways—none is more satisfactory than Leake's Tercentennial Edition, which with Keynes' Nonesuch edition, and Lier's publication, will probably remain the last word in Harvey editions for some time to come. From the new and vigorous Thomas press, this volume presents a novel format on excellent paper with the pleasing Caslon old style type.

Following a facsimile of the original Latin edition of 1628 is the author's translation, the third to be done into current English idiom. This is admittedly free and is designed to replace the somewhat stilted phraseology of Willis' standard English version, which, however, has been used as a "pony" guide. Occasional illuminating but not oppressive footnotes have been inserted. A comparison of the two translations soon convinces one that Doctor Leake has succeeded in his object of making Harvey's treatise more attractive to modern readers without loss of accuracy. A translator's postscript, a chronology of Harvey's life, and a rather scanty index conclude the volume.

E. K.

MODERN X-RAY TECHNIC. By ED. C. JERMAN. Pp. 260; 110 illustrations and charts. St. Paul, Minneapolis: Bruce Publishing Company, 1928. Price, \$5.50.

THIS book outlines simply some of the principles involved in roentgenography. The author has arranged at the end of some chapters a catechism which should greatly facilitate students of the branch of medicine and technicians. There are several conclusions drawn by the author that cannot be accepted without comment.

1. Registry of Technicians. It is questionable whether this registry should be supported by roentgenologists.

2. The Curved Bucky Grid. The late Dr. Caldwell was one of the early investigators of the method described for reducing the secondary radiations by a grid. He recommended a curved grid. The curved Bucky grid has some advantages that are not possessed by the flat Bucky, but the latter has a greater number of advantages over the curved, and is probably more universally used.

Except for some of the special examinations, the author has considered most of the routine examinations. The illustrations of the technique and the resulting roentgenogram are well illustrated. I have no doubt that this book will serve a useful purpose in supplying the need of students and technicians interested in roentgenography.

E. P.

PROBLEMS IN SURGERY. By GEORGE W. CRILE, M.D. Pp. 171; 49 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, \$4.00.

THE reader needs no introduction to the author of this little book. It is not a textbook in any sense of the word. It is rather a treatise on six different subjects, in every one of which the author is qualified to express an opinion. His first talk on management of acute infections is concise and to the point. The essay on the bad-risk patient lies well within the field that this writer has so extensively explored. The chapter on diagnostic and operative clinics is an excellent one. The Reviewer recommends the reading of this work by every one interested in better surgical results.

E. E.

NEUROLOGICAL EXAMINATION. By CHARLES A. MCKENDREE, A.B., M.D. Associate, Department of Neurology, College of Physicians and Surgeons, Columbia University; Associate Physician, Neurological Institute, New York. Pp. 280; 88 illustrations. Philadelphia and London: W. B. Saunders Company, 1928. Price, \$3.25.

THE study of the signs and syndromes shows lucid and inclusive treatment. A generous allotment of space for examination of the cranial nerves gives another valuable section.

As the reviewer sees it, the weakness of the book lies in the section on Mental Status, made distressingly short—12 pages out of 280—and at that, more than half of the subject matter is written by a psychologist, who further wastes space by padding her theme with historic data.

N. Y.

DIABETIC MANUAL FOR PATIENTS. By DR. HENRY J. JOHN. Director of the Diabetic Department and Laboratories of the Cleveland Clinic. Pp. 202; 42 illustrations. St. Louis: The C. V. Mosby Company, 1928. Price, \$2.00.

THIS book is another of a rather frequent type written for the diabetic patient. The author discusses among other things those

conditions that influence the course of the disease, the rôle of blood and urine sugar, insulin treatment and dietetics. At the end of the book there are the usual tables of food values and recipes. The subject is presented in a very lucid style that will permit the laity to obtain a knowledge of this condition. L. J.

A SHORT HISTORY OF MEDICINE. By CHARLES SINGER, M.A. M.D., D.LITT., Fellow of the Royal College of Physicians of London, Lecturer on the History of Medicine in the University of London. Pp. 368; 142 illustrations. New York: Oxford University Press, American Branch, 1928. Price, \$3.00.

LIKE all the author's medicohistorical writings, this book is fresh, thoughtful, interesting and correspondingly valuable. Even though it is a discussion of the principles of medicine from the historical standpoint more than a history of medicine in the traditional sense, it is a valuable adjuvant to such a history for the medical reader. It is addressed chiefly, however, to the intelligent layman. For him, more concerned with principles, sufficiently elucidated with cognate explanations, than with a detailing of all the strictly medicohistorical facts, it is even more valuable than a conventional history, with the added recommendation of moderate cost.

Following the chronologic approach, the author discusses in turn the medicine of Greece and its heirs, the Middle Ages, the Renaissance, the period of Consolidation (1700 to 1825) and the period of Scientific Subdivision (from 1825 on), to which last almost half the book is devoted. Emphasis is placed on the development of ideas rather than on the lives of those enunciating them, while the author's individual ideas, too, are often apparent. A vitalist in company with Aristotle, Harvey, Hunter, Claude Bernard, Joh. Müller and Virchow, he believes that "there is a principle in living things that cannot be expressed in physical or chemical terms." Recognizing that this is not a useful point of view in modern medical research, nevertheless he sees no reason for abandoning it as a point of view that makes existence intelligible. Certainly all must admit that mechanism, while contributing many useful scientific explanations, has thus far totally failed to explain life.

Together with a rational survey of an extensive field, the author has combined in small space a surprisingly large number of interesting historical facts and illustrations, many not easily available elsewhere. We heartily recommend the book to thoughtful medico and layman alike. E. K.

BOOKS RECEIVED.

NEW BOOKS.

- Report on Mussel Purification.** By R. W. DODGSON, M.D. (LOND.), M.R.C.P., (LOND.), M.R.C.S. (ENG.). Pp. 498; illustrated. London: His Majesty's Stationery Office, 1929. Price, £1 1s.
- Spinal Anesthesia.** By CHARLES H. EVANS, M.D. Pp. 203; 41 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$5.50.
- Harvey Lectures, 1927-1928.** Pp. 280; illustrated. Baltimore: Williams & Wilkins Company, 1929. Price, \$4.00.
- Malaria Problems.** By FREDERICK L. HOFFMAN, LL.D. Pp. 207. New York: Prudential Insurance Company, 1928.
- Thyroxine.** By EDWARD C. KENDALL, M.S., PH.D., D.Sc. Pp. 265; 38 illustrations. New York: The Chemical Catalogue Company, 1929. Price, \$5.50.
- Clinical Physiology.** By ROBERT JOHN STEWART McDOWALL, D.Sc., M.B., F.R.C.P. (EDIN.). Pp. 383; 4 illustrations. Philadelphia: D. Appleton & Co., 1928.
- Textbook of Clinical Neurology.** By M. NEUSTAEDTER, M.D., PH.D. Pp. 602; 228 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$6.00.
- The Story of Modern Preventive Medicine.** By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 295; 9 illustrations. Baltimore: Williams & Wilkins Company, 1929.
- Medical and Allied Topics in Latin Poetry.** By HEINRICH OPPENHEIMER, D.LIT., LL.D., PH.D. (LOND.), M.D. (HEIDELBERG), M.R.C.P. (LOND.). Pp. 445. London: John Bale, Sons and Danielsson, Ltd., 1929. Price, 30s.
- Surgical Clinics of North America. (Mayo Clinic Number) February, 1929.* Pp. 247; 141 illustrations. Philadelphia: W. B. Saunders Company, 1929.
- Spasmophilia.** By EDWARD C. WRIGHTSMAN, M.D. Pp. 155; 24 illustrations. Boston: Richard G. Badger, 1929.

NEW EDITIONS.

- An Index of Differential Diagnosis of Main Symptoms.** Edited by HERBERT FRENCH, C.B.E. (MILITARY), M.A., M.D. (OXON.), F.R.C.P. (LOND.). Fourth edition. Pp. 1171; 701 illustrations. New York: William Wood & Co., 1929. Price, \$18.00.
- The A B C of Hydrogen Ion Control.* Fifth edition. Pp. 132; illustrated. Baltimore: La Motte Chemical Products Company, 1929.
- A simple description of the colorimetric method of pH determination with its application to various commercial processes.

* Reviews followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Can the Gall Bladder Empty Through Duodenal Biliary Drainage? Is the Gall Bladder the Source of "B" Bile? A Cholecystographic Study of Biliary Drainage.—In 1917, the late Dr. Meltzer published in the AMERICAN JOURNAL OF MEDICAL SCIENCES an article upon disturbances of the law of contrary innervation in diseases of the bile duct and gall bladder, inserting at the end of his paper a foot note which read as follows: "In experiments with magnesium sulphate I observed that the local application of a 25 per cent solution of that salt upon the mucosa causes a completely local relaxation of the intestinal wall. It does not exert such an effect when the salt is administered by the mouth. The duodenal tube, however, apparently has reached an efficient practical stage. I therefore make the suggestion to test in jaundice and biliary colic the local application of 25 per cent solution of magnesium sulphate by means of the duodenal tube." This paragraph has occasioned a great deal of controversy in medicine in the past few years because of the clinical application of this suggestion of Dr. Meltzer, Lyon (*Arch. Int. Med.*, 1929, 43, 147) was the first to grasp the significance of this statement and through his earnest efforts the method suggested to drain the gall bladder has been extremely widely used throughout this country and Europe. However, there has been considerable controversy and discussion as to the merits and the value of this particular clinical procedure. In order, as the author says, to settle the question definitely, a study was made in association with Dr. Cole on the cholecystographic evidence of biliary drainage. At the same time a chemical study was made of the bile drained from the gall bladder by means of the duodenal tube. Before starting the account of his results, Lyon discusses briefly the surgical, experimental, cholecystographic and chemical proof that has been brought forth to show that the gall bladder contracts by its own intrinsic musculature and that secretory pressure, abdominal pressure and action of the sphincter play no important part whatever in this physiologic act of

emptying the viscus. In the present study 19 patients were selected for study, the idea being to make roentgenograms of the gall bladder sixteen or eighteen hours after the ingestion of tetraiodophenolphthalein. These people had or were presumed to have gall-bladder disease. Each one took a dinner rich in fat at 6.30 P.M. Three hours later they started the ingestion of the dye, a total of 3.5 gm. being given them. At 8 o'clock the next morning, the stomach being empty, a tube was passed, controlling the location of the bulb with the Roentgen ray after taking the gall-bladder picture. Thirty-three per cent magnesium sulphate, and in some cases 10 per cent peptone or 30 cc. olive oil, was injected through the tube. The bile was subsequently drawn through the tube and tested for iodine. Several hours later, after a fat rich meal, they were again examined by the Roentgen ray. Results: Four patients were discarded. The remaining 15 were divided into two groups. In Group I there were 8 patients who showed in practically every case a complete reduction in the size of the shadow of the gall bladder and in each patient there was a marked variation in the iodine content of the "B" bile and "C" bile. The "B" bile contained from 3.4 mg. of iodine per 100 cc. of blood to 9.6 mg., whereas the "C" bile varied between 0.42 and 3.2 mg. In the remaining 7 patients the results were not so satisfactory, due to the failure of the dye to show the gall bladder, inability of the patient to take the capsule satisfactorily, or for some other reason. While the reduction in the size of the shadow in these cases was not satisfactory, nevertheless, the iodine content of "B" bile was infinitely greater than the "C" bile. The author concludes as a result of the study that the question of genesis of "B" bile and "C" bile is definitely settled; that the gall bladder empties its contents by means of its intrinsic musculature; that good specimens of bile may be obtained by intraduodenal stimulation of magnesium sulphate; that specimens of gall-bladder bile are therefore procurable for chemic and bacteriologic study; and that we can now turn our attention to the investigation of the value of duodenal biliary drainage as an adjunct therapeutic agent in various problem diseases. The author has covered his subject well and has presented his work satisfactorily, so that in truth there can be no question as to the physiologic response of the gall bladder to intraduodenal stimulation. The only question of a controversial nature that he has not answered is: why gall-bladder drainage for the purpose of treatment, not diagnosis, when a fat-rich meal apparently may cause exactly the same sequence of events as the magnesium sulphate lavage?

Myocardial Disease and its Gastric Masquerades.—RIESMAN (*J. Am. Med. Assn.*, 1928, 91, 1521) presents some very timely words of warning to the gastroenterologists in reference to the frequency with which gastric symptoms obscure the true underlying pathologic process of disease. These observations are particularly pertinent when one remembers the tendency of the man limiting himself to a small specialty to neglect a thorough survey of the patient. Eight brief case reports are given, all of which are used for examples to illustrate the frequency with which cardiac disease produces evidence of gastric dysfunction. The obvious way of preventing these diagnostic errors, which might prove very serious, is to make a thorough examination of the patient, accepting neither his diagnosis nor the diagnosis of others as to his condition.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND
ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF
MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Treatment of Vertebral Tuberculosis by the Spine Fusion Operation.

—HIBBS and RISSER (*J. Bone and Joint Surg.*, 1928, 10, 805) states that the operative mortality was only nine-tenths of 1 per cent, all of whom were poor risks. It seems undoubtedly true that the results of this series would have been better if the cases had been operated upon early. Analysis of these facts shows that mortality and lowered resistance to tuberculosis is directly proportionate to the number of local manifestations of the disease. The percentage of deaths in the group having two spinal foci was 36, as contrasted with 26 in the entire series. Fifty per cent of the series complicated by hip-joint tuberculosis had a fatal termination and all of these who had tuberculous peritonitis or nephritis died. In that group, in which Nature had made an attempt at elimination of motion by an area of natural fusion of posterior vertebral elements, there were only 13 per cent of deaths and not one was due to tuberculous peritonitis. Thus it would seem that early elimination of motion in all diseased joints would increase the patient's resistance. Any treatment to be most effective in vertebral tuberculosis must be applicable to children, as most cases occur in children. Fusion takes place more rapidly in them and their recuperative powers are better. The enforced inactivity over long periods of time, so commonly used in the treatment of this disease in children is detrimental to their physical and psychologic development. Furthermore, there is no justification in the hope that all diseased joints become fused by such means. The diagnosis of tuberculosis of the spine should be possible very early, by Roentgen ray and physical examination. The hope of improving the results in the future depends upon the education of the medical profession in the methods of early diagnosis and upon their urging immediate operation.

The Blood Supply to the Appendix.—KOSTER and WEINTROB (*Arch. Surg.*, 1928, 17, 677) state that the macroscopic observations on the blood supply to the normal appendix show that the appendicular arterial tree is remarkably constant in its architecture. The definite determination of the supply into two layers, the richer of which is the deeper and the absences of a distinct blood supply to the mucosa are undoubtedly of physiologic importance. Attention is again drawn to the remarkable corkscrew and spiral character of the appendicular branches of the second, third and subsequent orders. From analogy with other organs

in which this type of vessel is found; for example, the uterus, intestine, urinary bladder, and so forth, this tortuosity speaks for a structure which is constantly changing in shape and in caliber. The next striking point about the blood supply is its richness and profuse anastomosis. This again is analogous to the condition found in organs subject to vascular obliteration, for example, the heart. The number of fat vessels found in the mesoappendix, seems to be out of proportion to that necessary to nourish a similar amount of fat and the close parallelism between the prominence of these vessels and the extent of the inflammatory process in the appendix suggests that these vessels play a compensatory rôle.

Diverticulosis of the Appendix and Pseudomyxoma Peritonei.—CHOYCE, RANDALL and GARDHAM (*Brit. J. Surg.*, 1928, 16, 62) note that the main interest of diverticulosis of the appendix lies in the relation of the condition to pseudomyxoma of the peritoneum. Diverticulosis of the appendix appears to be a condition of only moderate rarity. It can be said with certainty that diverticulosis of the appendix is a much less rare condition than pseudomyxoma peritonei. On the other hand, those cases of pseudomyxoma peritonei which have originated from the appendix have been shown in nearly all cases in which the appendix has been fully investigated, to be associated with diverticula. It appears then that diverticula of the appendix frequently, but not necessarily, lead to a pseudomyxoma of the peritoneum. It remains to decide the additional factor which must be present for a diverticulum to lead to pseudomyxoma peritonei. The presence in many of the recorded early cases of an omental mass in the region of the pseudomyxomatous appendix and the fact that pseudomyxomatous nodules in the omentum have come to be regarded as a characteristic sign in the early stages of the disease, suggest together that the omentum is closely connected with the production of pseudomyxoma peritonei.

An Experimental Study of Muscle Atrophy.—LIPPMAN and SELIG (*Surg. Gynec. and Obst.*, 1928, 47, 512) say that the muscle atrophy that follows the fixation of a limb is small in degree and is not appreciable before the lapse of at least a month. It is not comparable to the atrophy caused by nerve section, tenotomy and arthritis either as regard its onset or the proportions that obtain in these conditions. The atrophies that follow tenotomy, nerve section and arthritis are extremely rapid in onset and the progression is almost equally as brisk in all these conditions. The muscle atrophies that follow tenotomy and nerve section are due to cessation of muscle formation and are therefore, disuse atrophies. The atrophies that follow experimental arthritis are preceded by muscle relaxation, "muscle collapse" and the subsequent course is the same as that which obtains following tenotomy and nerve section. It is, therefore, reasonable to conclude that arthritic atrophy is also a disuse atrophy. The muscle disuse, however, is not caused by voluntary immobilization or external fixation, but is due to the "muscle collapse." Hence the theoretical and experimental evidence leads to the inference that although arthrogenic atrophy must be considered a disuse atrophy, it is not due to immobilization but it is caused by a reflex mechanism.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY.

Suprarenal Transplantation and Organotherapy in Addison's Disease.

—Fairly satisfactory results in the treatment of Addison's disease having been reported by a number of workers who administered large daily doses of fresh whole suprarenal gland, ERICH LESCHKE (*Med. Klin.*, 1928, 24, 1268) undertook to employ this treatment in a girl, aged twenty-eight years, suffering from a severe grade of Addison's disease presumably due to tuberculosis. After the treatment had been continued for four and a half months without any benefit, the patient had lost so much ground that the prognosis seemed hopeless. At this time the opportunity arose to obtain the greater part of a normal suprarenal gland from a patient at operation. This was implanted directly at the time of operation into a pocket in the abdominal muscles of the girl with Addison's disease. The results were extraordinary. The patient regained her appetite, her strength returned, the blood pressure rose from a level of 85 mm. to between 110 and 125, blood sugar became normal, and the skin pigmentation diminished rapidly. Menstruation which had long been absent appeared eight days after transplantation and has since worked regularly. There was also a marked growth of axillary and pubic hair. Shortly after transplantation it became impossible to continue the administration of fresh suprarenal glands as these could not be obtained, but treatment was continued with extract of the whole gland and injections of arsenic. Ten months after the transplantation the patient was still well and entirely without symptoms. Leschke suggests that the carrying out of such a procedure may give patients with tuberculosis of the suprarenal gland a sufficient period of restored health to permit a cure of tuberculosis and restoration of function in the remainder of the damaged gland and, may, therefore, offer considerable prospect of bringing about a permanent cure of the disease in a certain proportion of patients.

A New Procedure in the Treatment of Graves' Disease.—The well-established fact that residence in high altitudes is markedly beneficial to a large proportion of patients with exophthalmic goiter led HEINRICH LAX (*Klin. Wchnschr.*, 1928, 7, 2295) to carry out a series of very carefully controlled observations on the treatment of a group of such patients in a cabinet in which they could be subjected to reduced atmospheric pressure. Repeated accurate determinations of the basal metabolism were made upon all patients and a group was retained untreated to serve as controls. In addition to this method of control the treated patients were studied for a period of four days in the air chamber with the pressure remaining normal—a fact unknown to them. The patients selected for treatment comprised those with clinically

typical cases of medium to severe degrees. The basal-metabolism readings before treatment varied from +30 to +100 per cent. Each patient was exposed daily to the reduced pressure treatment for a period of four hours and the treatment was continued for from two to three weeks. Forty patients were so treated; all other forms of therapy having been omitted for a period of four weeks prior to the institution of treatment. Of these 29 showed pronounced reduction in the basal metabolism, several became normal, and marked improvement was shown in the subsequent symptoms of the disease. These patients were observed for second periods of time up to nine months during which they maintained the improvement in most cases. Several patients who failed to improve were later sent to high altitudes where they also showed no response. The author believes that the rapid and temporary reduction in atmospheric pressure as produced in these cases is perhaps more beneficial than prolonged residence at a high altitude and he is under the impression that still better results are obtained when the atmospheric pressure in the chamber is suddenly changed several times during each period of exposure. He feels that these results indicate that the chief virtue of treatment in high altitudes is due to the reduction of atmospheric pressure. While holding this view he admits that other benefits result from residence in high altitudes but he feels that a preliminary period of treatment and observation in the reduced-pressure cabinet is of great value both as a therapeutic measure and as a method of determining in advance whether or not a patient should be sent to a high altitude.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Asthma in Children.—PESHKIN and FINEMAN (*Am. J. Dis. Child.*, 1929, 37, 39) have compared the application of local passive transfer of human hypersensitiveness or the indirect method with the scratch and intradermal skin tests or the direct method. They tested 18 asthmatic children from seven months of age to fourteen years by each method, using 33 protein extracts. They used dried powdered extracts for the scratch tests and fluid extracts for the intradermal test. These children were watched over a period of two years. The total number of tests performed in this series was 3252. The total number of positive reactions ranging from questionable to 4+ obtained by the scratch technique with the direct method was 92. On checking up this group only 18 reactions were found in the same cases with the indirect method. The total number of positive reactions ranging from positive to 3+ obtained by the intradermal technique with the direct method was 104. Checking these cases with the indirect method, only 24 positive

reactions were obtained. Comparative tests between the scratch and intradermal technique with both the direct and indirect methods showed that the total number of positive reactions obtained by the scratch technique with the direct method was 92. Of these 80.5 per cent were negative with the indirect method. The corresponding tests with the indirect technique by the direct method showed 50 positive reactions. Of these 83.5 per cent were negative with the indirect method. The total number of negative reactions obtained by the scratch technique with the direct method was 496. Of these 3 per cent were positive with the indirect method. The corresponding tests with the intradermal technique by the direct method failed to give positive reactions with the indirect method. Three children with asthma and hay fever reacted negatively to pollen with both the direct and indirect methods of testing. They gave positive reactions by the conjunctival tests with the dry powder. This result emphasizes the value of the latter-mentioned technique which Peshkin previously claimed to be a rapid safe and reliable method in patients refractory to skin tests. The indirect method of testing employed as a routine measure, according to these authors, is unsafe and they feel that its employment as a substitute for the direct method even in especially selected cases is not practical.

Skin Reactions of Patients with Rheumatic Fever to Toxin Filtrates of Streptococcus.—SWIFT, WILSON and TODD (*Am. J. Dis. Child.*, 1929, 37, 98) state that patients with rheumatic fever gave a higher proportion of positive skin reactions with filtrates of both indifferent and green streptococcus than did the non-rheumatic controls. Cases with active rheumatic fever gave a higher proportion of positive reactions with these filtrates than did those with inactive or cured rheumatic fever. Comparing the reactions with unheated filtrate with those with filtrates boiled for one hour, it was found that the boiled filtrate gave stronger reactions in most patients with rheumatic fever and weaker reactions in most patients with inactive or cured rheumatic fever. They did not find a close correspondence in the capacity of patients to give skin reactions with Dick toxin and filtrates of non-hemolytic streptococci. Positive reactions in patients with rheumatic fever seemed to depend more on the state of hypersensitiveness to certain products of streptococci than the specificity of any one type of streptococcus.

Congenital Stenosis of the Esophagus.—BEATTY (*Brit. J. Child. Dis.*, 1928, 25, 237) reviewed the literature comprising 50 cases of the congenital stenosis of the esophagus and adds 5 cases in his own experience. This anomaly is rare and there are two types. One is a membranous type, in which there is partial occlusion of the lumen by a fold of normal mucous membrane. The other is a nonmembranous type in which there is a localized reduction in the size of the esophagus. The stenosis may be situated anywhere in the esophagus, but the most common sites are in the lower and upper ends. The congenital type is characterized by an absence of pathologic changes in the walls of the esophagus in contradistinction to the acquired form of stenosis. There may be however, hypertrophy and dilatation above the obstruction. Other congenital abnormalities do not usually accompany this condition.

The onset of symptoms is usually in infancy, more commonly at the time of weaning. The most characteristic is the regurgitation of food unchanged in form within a few minutes after swallowing, and this is not associated with pain or nausea. Adult patients may be well developed and well nourished but some degree of infantilism so common in children and adolescence. In diagnosing this condition, Roentgen ray and endoscopic examination are most helpful. The prognosis in the membranous type is good when treatment is proper and complete recovery usually follows. In the non-membranous variety, the outlook is not unfavorable as regards life and some of the patients live to an old age, but in the latter form, the relief of symptoms is more difficult and severe restrictions in solid food are generally necessary throughout life. In treating the membranous variety, gradual dilatation with bougies is checked by endoscopic examinations until the membrane has been destroyed. In the non-membranous form, dilatation is likely to be successful, but is attended with considerable risk of rupture. In stenosis at the lower end, excision may be considered.

Classification of Heart Disease in Children.—WILSON, LINGG and CROXFORD (*Am. Heart J.* 1928, 4, 197) observed 500 children ranging in age from two to twenty-two years and he found that four-fifths presented a history of rheumatic disease. Congenital heart defects occurred in 50. In 18 of these there was subsequent rheumatic infection. Children with possible heart disease, where systolic murmurs were heard between the second and fourth interspaces, retained the same physical signs without progress over a period of years. They found that the average age at the onset of the rheumatic infection was 7.3 years. In half the children the onset occurred between the ages of six and nine years. Rheumatic infection is principally seen in children of the grade-school age. It has been observed that from the age of twelve years the tendency to infection diminishes. Three-fourths of 413 children with a rheumatic history developed definite heart disease and the remaining one-fourth were potential heart-disease patients. The heart is probably always involved to some extent at the time of the first infection, although marked involvement was noted in only 63 per cent within one year of the onset. The associated manifestations of rheumatic infection were not indicative of the degree of heart involvement. Growing and joint pains seemed to bear the same relationship to heart involvement as polyarthritis or chorea. The degree of heart involvement was closely related to the number of attacks of carditis. In this series 12 per cent of the children died and 88 per cent of these deaths were due to rheumatic heart disease.

The Value of Parathyroid Hormone for the Organism.—WALTNER (*Monatschr. f. Kinderh.*, 1928, 40, 317) gives as one of the causes for rachitic disturbances in calcification the hypertrophy or increased function of the parathyroid glands. Increased function of the parathyroid glands in rickets mobilizes calcium from the bones or hinders the normal deposit of lime. With a marked decrease in the function of the parathyroid and a positive calcium balance, disturbances of the osseous system will occur. Experiments show that excess as well as deficiency of parathyroid hormone causes a change in the bones. The presence of a

certain amount of parathyroid hormone is necessary for a normal development of the skeleton. Removal of the parathyroid glands means absence of parathyroid hormone, and the blood cannot keep enough calcium absorbed in the intestines but deposits it into the soft tissue. Animals without parathyroid glands develop osteoporosis. When parathyroid hormone is present in excess, an increased consumption of calcium is the result. Calcium is particularly taken away from the osseous system. It can be seen from this that an excess of parathyroid hormone has the same effect as the lack of hormone. The phenomenon is analogous to the effect of insulin on the production of glycogen.

Paroxysmal Sneezing as an Equivalent of Paroxysmal Cough of Pertussis.—REICHLE (*J. Am. Med. Assn.*, 1929, 92, 443) reports two cases and refers to a number of authorities. He feels that sneezing, if paroxysmal in character, may be of great value in diagnosing as an early symptom of pertussis. In certain young children the sneezing may supplant the cough either entirely or partly. These attacks of sneezing are typically convulsive, cause congestion of the head, cyanosis and exhaustion, and may end in expectoration of the usual tenacious mucus through the mouth and nose, as in the cough attacks. These spasms may be accompanied by coryza, inspiratory crow and vomiting. The cases reported in this article as well as those described in the literature have been moderately severe but not fatal.

DERMATOLOGY AND SYPHILIS

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Pathogenesis of Trichophytids. SULZBERGER (*Arch. Dermatol. and Syph.*, 1928, 18, 891). This article contains a succinct and clearcut explanation of the present conceptions of the mechanism of development of trichophytids or secondary general eruptions associated with an allergic state of the individual following the development of a deep lesion due to fungus infection. The report covers the experimental production of hematogenous infection and the development of spontaneous lesions in guinea pigs. Following intracardiac injection, the fungus was recovered from the blood stream at two distinct periods; that immediately following the injection, and again ten to thirteen days later. The second appearance of the organism in the blood stream is interpreted as spontaneous and as corresponding to the development of the allergy which is instrumental in the production of trichophytids. In 3 of 34 guinea pigs examined, the organism was recovered from the viscera (spleen and kidney).

Superficial Yeast Infections of the Glabrous Skin.—WHITE (*Arch. Dermatol. and Syph.*, 1928, 18, 429) reports further on *Cryptococcus* (yeast) infections of the skin. Reference is had to the observations of Castellani (1927), Greenbaum and Klauder (1922), Beeson and Church (1926). The involution of artificially induced fungus lesions can be materially delayed, and their extension promoted by mechanical irritation, such as occurs with scratching. While *cryptococci* inhabit normal skins, a limited series of successful inoculations of cultures on their respective hosts indicates their possible pathogenicity in the syndrome known as seborrheic dermatitis, especially of the exudative type. The postulates of Koch have been fulfilled; the organism was recovered from the artificial lesion. It is suggested that some examples of infantile eczema may belong in this group.

Cryptococcus Epidermica.—WHITE and SWARTZ (*Arch. Dermatol. and Syph.*, 1928, 18, 692) ascribe cutaneous infection with the *cryptococcus* to poor hygiene, particularly the wearing of unboilable clothing next to the skin. They differentiate the disease which they believe to be an entity, from eczema as such; soap eczema of Radcliffe Crocker; psoriasiforme eczema of Brocq; aberrant pityriasis rosea, which its patchy character and dry lesions may resemble; erythrodermie pityriasique en plaques disseminees; premycotic mycosis fungoides; tinea versicolor; and epidermophytosis. They treat it with an ointment containing mercurochrome 0.68 gm.; salicylic acid 2 gm.; petrolatum and hydrous wool fat, each 16 gm.—with varying degrees of success.

Hot Baths in Late Syphilis.—HOLLINGSWORTH (*Arch. Dermatol. and Syph.*, 1928, 18, 736) directs attention to the ancient lineage of this procedure and records its inapplicability to 5 cases which were treated by this method with weakening effects, and no significant therapeutic response. The reported experiments on rabbits do not encourage the belief that the method will be applicable to human syphilis. Massa, in 1563, summarized the situation and dismissed the procedure in words applicable today.

Serologic Discord in Latent and Treated Syphilis.—SHEPLAR, LYONS and MACNEAL (*Arch. Dermatol. and Syph.*, 1928, 18, 742) compared a Wassermann procedure using the Kolmer and a cholesterinized beef-heart antigen, with the Kline, Kahn and the Vernes procedures. They found that by making up their series from nonsyphilitics and patients with untreated early syphilis it was possible to secure from 90 to 95 per cent agreement in the results of the three procedures. On the other hand, if the series were made up from treated and latent syphilitic patients, irreconcilable differences between the results of the tests developed. To this they apply the apt term "serologic discord." They suggest that the variations observed in the testing of a single serum are due to the fact that there is not one but a number of antigenic elements in variable proportion in the serum of the latent and treated syphilitic patient and that each test procedure singles out or reacts to certain of these, producing a variability in results that must be met by the use of several test methods in examining of each serum.

Antenatal Treatment of Syphilis.—NABARRO (*British J. Ven. Dis.*, 1928, 4, 107) reviews the literature of the subject and the article is correspondingly difficult to abstract. Significant points may, however, be quoted. Antenatal treatment of the syphilitic mother dates to the 17th century. Johnson, in 1877, wrote on the subject in the United States. The results of Boas and Gammeltoft, published in 1925, are the most complete in Europe. The period of observation of the healthy children ranged from six months to fifteen years. The following table is a valuable summary:

Treatment of mother.	No. of cases.	Children (per cent).	
		Syphilitic.	Healthy.
Syphilis not treated	201	96.5	3.5
Mercury before pregnancy; no treatment during	87	90.0	10.0
Arsphenamin before pregnancy; no treatment during	15	80.0	20.0
Mercury during pregnancy	111	72.0	28.0
Arsphenamin before pregnancy, mercury during	26	27.0	73.0
Arsphenamin during pregnancy	98	19.5	80.5
Arsphenamin before and during pregnancy	7	14.5	85.5

Ballantyne from the Royal Maternity, Edinburgh, reports 5.1 per cent stillbirths in 138 supervised and treated syphilitic mothers as compared with 60.6 per cent stillbirths in 33 untreated mothers. Nabarro examines the child every three months the first year, twice the second and third years and once annually thereafter. It has been shown that a woman may give birth to a syphilitic child twenty, twenty-four, twenty-six and even thirty-seven years after infection. In the Boas and Gammeltoft series, 55 of 483 pregnancies in untreated syphilitic women produced 48 syphilitic and 7 healthy children from four to twenty years after infection. Observers agree that the mother should be treated during each pregnancy and early in the course of the pregnancy if the child is to receive the greatest possible protection.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Results of Olshausen Suspension Operation.—One of the simplest operations for the suspension of a retroverted uterus is that which has been described by Olshausen and which consists of suturing the round ligaments to the abdominal wall. In order to determine the end results of this operation, BARROWS (*Am. J. Obst. and Gynec.*, 1928,

16, 61) has made a comparative study of this operation and the Baldy-Webster and Simpson-Montgomery types of operation. Of 135 Baldy-Webster operations, 109 were traced with 88 per cent excellent results; of 211 Simpson-Montgomery operations, 164 were traced with 93 per cent excellent results; of 571 Olshausen operations, 432 were traced with 92 per cent excellent results. In this series of 571 Olshausen operations there were 7 infected wounds, the silk ligature had to be removed in 1 case, a round ligament pulled away from the abdominal wall in 3 cases, there was one sinus in the abdominal incision and in 2 cases there was a potential hernia near the site of the knot. The author states that by using the braided-silk ligature doubled, one is able by tension in tying the knot to cause sufficient application of the round ligament to the solid structures of the abdominal wall without serious trauma to the ligament or danger of cutting through its muscular tissue. In spite of the fact that previous descriptions of the operation have stressed the tight tying of the silk knot, he believes that it is important not to tie the ligature tight enough to cut through the ligament early or late and that many failures have been avoided on this account. Briefly, therefore, his analysis of the situation showed that the operation compares favorably with the other types of round ligament suspension, including its reaction to pregnancy. In spite of theoretical objections to the technique of the operation, it is seldom followed by intestinal obstruction, the silk ligatures rarely give trouble, while the ease and rapidity of accomplishment as well as the absence of unnecessary trauma to adjacent structures recommend the operation.

Extraction of Hair Pin from Bladder.—The various types of foreign bodies which have found their way into the female urinary bladder would make an interesting museum exhibit at a hardware show and one of the commonest articles is, as may be supposed, that universal tool of the female of our species, the hair pin. Without going into the details of why it gets into the bladder so frequently, it might be of value at some future time to be aware of the method which SIGWART (*Zentralbl. f. Gynäk.*, 1928, 52, 1550) employed for the removal of a hair pin, especially when an operating cystoscope and forceps are not available. Having located the pin through the cystoscope, he took an ordinary ureteral catheter and cut off the tip of it. The wire stylet which is supplied with the catheter was then passed through its lumen and a loop made on the distal end of the wire after it had passed through the catheter. This loop was made small enough to pass through the catheter channel of the cystoscope, yet large enough to slip over the end of the hair pin. After introducing this catheter into the bladder through the cystoscope, the loop was slipped over one of the ends of the hair pin and then gently worked upward until it was at the center of the elbow of the pin. The cystoscope was then withdrawn over the catheter and then the catheter was gently pulled through the urethra, drawing the hair pin after it without causing the patient any pain.

Cause of Uterine Myoma Sterility.—From the Gynecological Institute of the Kyoto Imperial University comes an interesting experimental study by UCHIGAKI (*Jap. J. Obst. and Gynec.*, 1928, 11, 61) who investigated the cause of sterility in cases where there is a very small myoma,

almost impalpable, after the removal of which the patient easily conceives. These growths are so small that it is hard to explain the sterility on a mechanical basis. Working with rabbits, he found that the continual injection of an extract prepared from a myoma causes atresia and degeneration of the ovarian follicles, weakness of the muscular layer of the uterus and degeneration in its mucous membrane. These injections markedly accelerated the movements of the excised uterus and atropin and scopolamin have no controlling power over this acceleration so that the point of attack of these extracts is presumably in the muscles themselves. When rabbit were impregnated and then given these injections they usually failed to conceive. In another experiment, simple laparotomy was performed with instant closing of the abdomen and copulation was effected after a certain period of time. In 6 cases, there were 4 instances of conception. However, in 6 other rabbits a piece of cartilage was transplanted into the wall of the uterus to simulate the foreign body action of a myoma and none of them conceived. After the cartilage was removed, 2 of them conceived. The experiments were all well controlled and Uchigaki concludes that the toxic influence of the myoma element on the ovarian follicles, its acceleration of the muscular activity of the uterus and the circumscribed presence of myoma nodules acting as foreign bodies are all factors in the production of the sterility associated with uterine myomata.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Concerning the Etiology of Postoperative Abscess of the Lung: A Review.—As a pathologic entity, pulmonary suppuration embraces a variety of acute and chronic lesions, capable of differing greatly in their mode of production, their morphologic characteristics, and their response to treatment. One of the outstanding manifestations of pulmonary suppuration is abscess which also may occur in various forms, each of which may be due to quite different causes. Among the commoner types of lung abscess is that which is now recognized as developing after surgical procedures. It has been estimated that approximately one-third of nontuberculous abscesses of lung follow operations (Wessler, 26 per cent; Lockwood, 43 per cent; Heuer and MacCreedy, 26 per cent; Homans, 57 per cent; Singer and Graham, 32 per cent; Lambert and Miller, 25 per cent; Whittemore, 66 per cent; Hedblom, 21 per cent; Lord, 42 per cent; Cutler and Schlueter, 29.6 per cent [515 of 1908 cases collected from literature, including those given above]). Of the postoperative pulmonary abscesses, a relatively high proportion have followed tonsillectomy. For example, in further analyzing the statistics of the authors just mentioned, one finds that the

percentage varies from 25 to 80 (Wessler,¹ 80; Lockwood,² 70; Heuer and MacCreedy,³ 25; Homans,⁴ 54; Singer and Graham,⁵ 73; Lambert and Miller,⁶ 52; Whittemore,⁷ 72; Hedblom,⁸ 32; Lord,⁹ 51; and Schlueter and Weidlein,¹⁰ 52—the same collected series previously reported by Cutler and Schlueter¹¹). This apparently high frequency (circa 50 per cent) has resulted in the idea that pulmonary abscess, as a postoperative complication, is virtually peculiar to tonsillectomy. As a matter of fact, however, closer investigation does not substantiate this conception. The relevant statistical data, compiled from provincial sources, reveal a wide variance in the incidence of posttonsillectomic abscess of lung—varying from none in 20,000 and 3500 cases by Lyman,¹² and Crowe and Scarff,¹³ respectively, to two in 20,000 by Hedblom⁸ and two in 12,045 by Herb,¹⁴ to the astonishingly high calculation of one in every 358 tonsillectomies (Glowacki¹⁵). On the other hand, Moore,¹⁶ after a comprehensive national survey comprising about 450,000 cases, found that pulmonary abscess occurred once in every 2500 operations for the removal of tonsils. Moreover, it must be kept in mind that tonsillectomy is a very common operation, as a recent governmental report¹⁷ has shown, and that “about one-third of all operations since 1924 among the American urban population were for the removal of tonsils and adenoids.”¹⁸

Nevertheless, while it may be true that lung abscess is a relatively infrequent posttonsillectomic complication and that it follows this operation no oftener than surgical procedures in any other septic field, its actual incidence is so alarmingly high as to become a serious problem. The realization of this has stimulated an unprecedented activity in clinical and investigative fields, not only of otolaryngology but also of many other departments of medicine and surgery, with a view to obtain a clearer understanding of the factors involved so that appropriate prophylactic and remedial measures might be ascertained.

While these studies have embraced practically all of the salient phases of the subject, most of them have been motivated by the desire to determine the ways in which the infection can be transported from the operative site to the lung. Without delving into detail, it can be said that the results of these researches have evolved two outstanding theories regarding the *modus operandi* of postoperative pulmonic abscess, namely, the “aspiration” and the “embolic.” Naturally, the former has to do with the respiratory and the latter with the cardiovascular system. Although Smith¹⁹ says that “at present each (theory) has about an equal number of adherents,” Schlueter and Weidlein²⁰ state that “in a census of recent writers, forty declare themselves in favor of aspiration, while only ten favor embolism as the direct cause of lung abscess.”

As the rivalry between these two schools of thought is keen; as the controversy is acute; as the champions of each emphatically maintain that the solution to the problem is of cardinal importance in pointing the way to the prevention of this dread posttonsillectomic sequela; and as Smith¹⁹ puts it, “the evident conflict between these theories is an obstacle to the adoption of satisfactory methods of prevention,” the purpose of this communication is to present, briefly, the findings of the more recent available investigations pertinent to the question.

"Embolic" Investigations.—In 1923, Fetterolf and Fox²¹ studied the reaction of the paratonsillar tissues in recently tonsillectomized dogs. Inasmuch as they found areas of hemorrhage and necrosis, bacteria, and sterile or septic thrombi in the traumatized bloodvessels, they concluded that "while realizing that posttonsillectomy lung complications may at times be of inspiratory origin we believe that such origin is not as common as has been thought," and considered it quite possible for small emboli from the operative wound to cause septic infarcts in the lung.

Recognizing the important part played by emboli in the causation of other types of postoperative lung complications, as suggested by Mikulicz,²² and believing that pulmonary abscess might have a similar etiology, Cutler and Schlueter¹¹ and their co-workers, Holman,²³ Weidlein,²⁴ and Holloway²⁵ have conducted numerous experiments on dogs "in the hope that further proof might be found for the concept that a large proportion of such complications are due to embolism from the operative wound."²⁶ By liberating into the venous circulation artificially enclosed septic emboli, they were able to produce abscesses of the lung with great regularity. In view of the fact that their attempts to cause lung abscess by the intrabronchial injection of infected materials failed, they believed that their results furnished further evidence in favor of the embolic theory of pulmonary abscess.

Because such abscesses in the experimental animal differed from those commonly found in human beings in their failure to become chronic, and considering the factor of chronicity to be of major importance, Herrmann and Cutler²⁷ succeeded in inducing chronic abscesses in the canine lung by the introduction, according to the standardized technique, of emboli infected with material from the lesions of human pyorrhea alveolaris. The authors regarded their findings as indicating that chronicity of the experimental canine pulmonary abscess is dependent upon the presence of a certain group of anaërobic bacteria frequently encountered at the gingival margins in pyorrhea.

Further experimental observations concerning such factors that might determine chronicity as cough, foreign bodies and types of microorganisms have been reported by Weidlein and Herrmann.²⁸ After investigating both the respiratory and circulatory routes of infection, they concluded that while the action of cough, as described by Brown and Archibald,²⁹ exerts a determining influence on the chronicity of pulmonic suppurative processes, it alone is not able to account for the duration of the lesions as found in man; that the rôle played by a foreign body as a source of irritation is probably a minor one unless actual injury to the bronchial wall results; that the presence of certain anaërobic bacteria (spirochetes, vibrios and fusiform bacilli) is of importance in the production of lung abscess; and that it is doubtful whether pulmonary abscesses can be produced by the introduction of material into the respiratory tree under conditions of only partial occlusion. These workers also state that "whether these infectious agents reach the lung in man by way of air passages or the blood stream is still a debatable point. However, under experimental conditions, insufflated material must actually block the air passages completely, as well as injure the bronchi, before an abscess can be produced."

Regarding the bacteriologic phases of the subject, it has been demon-

strated that the duration of a pulmonic abscess may be influenced not only by the immunological attributes of the host, but also by the nature of the causative microorganisms. For instance, van Allen³⁰ has shown that abscesses, experimentally produced by *Staphylococcus aureus*, heal within four weeks; that, according to Holman, Chandler and Cooley,³¹ a mixture of the usual pyogenic bacteria prolongs the healing time; and that abscesses resulting from fusospirillary forms persist as long as two or three months (Weidlein and Herrmann²⁸). These fusospirillary organisms are virtually ubiquitous in the oral cavity, being found in great numbers at the gingival margins and in the actinomyces—like granules of tonsillar crypts, as well as in pulmonary abscess and gangrene (Davis,³² Pilot and Davis,³³ Pilot and Bram,³⁴ Pilot, Davis and Shapiro,³⁵ and Pilot and Davis³⁶).

In order to ascertain whether a lung abscess infected with an organism commonly associated with only acute lesions may be rendered slow to heal by the superimposition of bacteria which are capable of causing chronic pulmonary processes, Adams, van Allen and Day³⁷ produced lung abscesses in dogs by the embolic method described by Cutler *et al.*,^{11,23} and then introduced, intratracheally, sputum freshly obtained from individuals with chronic pulmonary suppuration. It was found that staphylococcic abscesses, which regularly heal before thirty days, frequently persisted for a longer period. The authors raise the question whether in man postoperative lung abscess which occurs from infected embolus may become superinoculated by mouth organisms through accidental insufflation, and thereby assume the characteristics of bronchogenic abscesses.

(To be concluded in May issue.)

RADIOLOGY

UNDER THE CHARGE OF

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Fusospirochetal Pulmonary Gangrene.—Two cases are reported by DOUB (*Radiology*, 1928, 11, 333). One occurred after operation for inguinal hernia and the patient died. In the second case the disease came on independently and the patient recovered after evacuation of a pulmonary abscess and cauterization of the abscess cavity. An abscess was revealed by the Roentgen ray in both instances. Fusospirochetal gangrene has become a recognized clinical entity in recent years. Bacterial studies of the sputum reveal fusiform bacilli, spirochetes and other bacteria, especially streptococci. Experiments indi-

cate that these organisms are saprophytic and that devitalized tissue is necessary for their growth. Clinically the disease simulates a bronchitis or bronchopneumonia except that the sputum is always fetid. Roentgenologically the lesion resembles an abscess or gangrene, but it progresses more rapidly than an ordinary infection. Administration of arsphenamin is the accepted treatment in the earlier stages, and operation in the later chronic stages.

Radiotherapy in Actinomycosis. Approximately 30 cases of intra-abdominal or intrathoracic actinomycosis have been observed at the Mayo Clinic from 1920 to 1925, and these are reported in tabular form by DESJARDINS (*Radiology*, 1928, 11, 321). In 26 cases the disease affected chiefly the intestinal or pelvic structures. Thoracic structures were the principal seat in 11 cases and in 7 the lesions were in both the thorax and abdomen. Treatment in most cases consisted of a combination of drainage, the administration of iodides internally and Roentgen irradiation of the abdomen or thorax. Radium was also given at some time in 8 cases. When actinomycosis attacks the intestine or lungs the disease often becomes extensive before its character is recognized. It is not surprising, therefore, that the series shows a very high mortality. Nevertheless, the therapeutic combination commonly resulted in amelioration, and several patients were apparently well after one or two years.

Clinical Difficulties Encountered in Cutaneous Roentgen Therapy.—Objectionable conditions that are characteristic of many skin diseases are often attributed to treatment with Roentgen rays or radium, says MACKEE (*Am. J. Roent. and Rad. Therap.*, 1928, 20, 121). Spontaneous exacerbations of certain diseases are common, topical remedies may cause alarming symptoms, additional affections may develop and a number of dermatoses have objectionable, disfiguring and even dangerous sequelæ which may erroneously be attributed to irradiation. The author, therefore, thinks that irradiation treatment should be conducted or supervised by a dermatologist. Its intelligent use requires a thorough training in cutaneous medicine. It is important to know what dermatoses are amenable to irradiation and what the therapeutic response should be. Such knowledge will do much to prevent useless or harmful treatment. If a disease fails to yield to the Roentgen ray or radium in a normal manner they should be discontinued and all the resources of cutaneous medicine employed to combat the affection. In fact, it is preferable to depend on these resources as much as possible in every case and from the beginning of treatment.

Osteochondritis Dissecans.—Observation of several cases of osteochondritis dissecans in unusual situations is the basis of a paper by GEYMAN (*Radiology*, 1928, 11, 315) on this subject. The most commonly reported sites are the lateral portion of the mesial condyle of the femur and the external condyle of the humerus. In the author's first case a fragment of bone had become detached from the mesial articular facet of the patella near the distal border, leaving a small oval defect in the patella which was visible in the roentgenogram but overlooked prior to operation. In the second case the fragment had come from

the lateral portion of the external condyle of the knee. The third case was one in which the left hip joint was affected; roentgenograms revealed a rather large area of subchondral rarefaction in the head of the femur, and within the cavity lay an apparently completely separated bony fragment. In the fourth case the defect and fragment *in situ* were in the external condyle of the humerus. A history of trauma was obtained in 3 of the 4 cases.

Roentgen Studies of the Bones in Certain Diseases of the Blood.—In several cases observed by KARSHNER (*Am. J. Roentgenol. and Rad. Therap.*, 1928, 20, 433) at the Children's Hospital, roentgenograms of the bones have aided the diagnosis of certain diseases of the blood. In von Jaksch's anemia—anemia infantum pseudoleukemica—there is a decided thickening of the medullary portion of the cranial bones, with thinning of the outer and inner tables. Early the bone marrow is mottled and spongy; later striations of new bone perpendicular to the tables appear. The pelvis, spine, ribs, scapulæ and bones of the hands and feet are very porous; the metacarpals are expanded; the cortex of the long bones is very thin and the medulla is unusually transparent. In a case of leukemia just before death, there was a slight rarefaction of the larger bones. The periosteum of both humeri and femora was raised, and in places new bone was laid down perpendicular to the shaft. The only positive Roentgen ray finding in a case of chloroma was widening of the cranial sutures, the long bones being negative. The Roentgen ray changes of hemophilia are the result of hemorrhage into the joints and adjacent bone. Any joint may be involved, most commonly the knees, elbows, ankles, hips and shoulders. In the early stage there may be effusion of blood into the joints with or without calcification. The joint capsule may be thickened and there may be lipping similar to that of hypertrophic arthritis.

NEUROLOGY AND PSYCHIATRY

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Lipodystrophies: Report of Seven Cases.—LLOYD H. ZIEGLER (*Brain*, 1928, 51, 147) presents the clinical histories of 7 patients with lipodystrophic disturbances. He considers nervous symptoms of varying degree and nature to be common to the group. Five of the 7 cases either had, or showed some signs tending toward, diabetes mellitus. He states that the chief hypothetical causes are neurotrophic and endocrine disturbances, alteration of fat metabolism, race and heredity,

infection and congenital defect. As to treatment, he reports that paraffin injections to remedy the facial appearance have not been permanently successful. A few patients have been benefited by rest in bed, ovarian extract and whole pituitary.

The Clinical Differentiation of Psychogenic and Physiogenic Disorders.—R. D. GILLESPIE (*Brain*, 1928, 51, 254) records 9 cases in which the differentiation of a psychogenic from a physiogenic disorder presented a serious difficulty. In a study of 13 cases he found 9 erroneous diagnoses of which 5 were of organic disease where only psychogenic symptoms were present and in 4 a diagnosis of psychogenic disorder was made when the condition was one of organic disease. He advances the following criteria for differential diagnosis. (1) The nature of the physical signs present. If the physical signs are relevant to the complaints it is not necessary to go further for diagnosis except for the purpose of assessing any suspected psychogenic element in the disability produced. If the physical signs are not apparently relevant it is necessary to investigate further. "There is a presumption of psychological origin for all physical signs that may be produced either by the direct effect of emotional disturbance or by the patient's volition." (2) The type of history of the illness. He states that there are common types of history that are indisputably those of a physical disorder. "Where the onset of certain signs and symptoms coincides in time with certain events, it is justifiable to suspect strongly an association between the two. Where there is a repeated coincidence of symptom and provocative situation, the suspicion is strengthened." (3) "A general setting of psychic disequilibrium is necessary for the development of a psychogenic disorder in response to external factors." (4) The personality make-up of the patient is of great importance as aberration from the average types of personality weigh the balance in favor of the psychic origin of the illness. (5) The mental attitude of the patient to his signs and symptoms. The neurotic shows deviations from the normal attitude either in an excess or defect of concern, together with a lack of persistence and determination in carrying out therapeutic recommendations. (6) The purpose which the illness seems to fulfill. "Where there seems to be nothing but disadvantage accruing, and when there is little discoverable cause for dissatisfaction . . . the psychic origin of symptoms must be doubtful. But even where a definite advantage seems to be gained, this may be an accident."

Are the Feeble Minded Criminals?—WALLACE (*Ment. Hyg.*, 1929, 13, 93) calls attention to the fact that when the class of feeble minded included only idiots and imbeciles the term crime was almost unknown in the field of mental deficiency. With the advent of intelligence tests and discovery of the moron group criminality in connection with the feeble minded became conspicuous. He states that if feeble mindedness in itself is a cause of criminality the two should appear in direct ratio and the greater percentage of criminals should be found in the lower grades of the feeble minded. The high percentage of feeble minded in the delinquent and criminal class (15 to 30 per cent) he believes would be modified by considering certain important factors that have a bearing upon the discovery and confinement of delinquents. First of all, there

is a large number of individuals who are not delinquent but whose mental level would place them in the feeble-minded group. Also the greater number of feeble minded who are delinquent are quickly discovered while a large percentage of persons of normal intelligence escape. Especially he believes this to be true in the case of illicit sex practices among girls. Again, the feeble minded have neither influential relatives to intercede for them nor the ability to adequately defend themselves. He would divide mental defectives who come in conflict with the law into two groups: "Delinquent defectives" in which the mental defect is the major abnormality; and "defective delinquents" in which the delinquency is the primary consideration and in which the defect is primarily in the field of social adjustment. "If two cross sections of the population could be studied from a psychiatric point of view with the object of ascertaining what material it is that makes for positive, active criminality, it is doubtful if the greater preponderance of that material would be found in the section of the population whose mental levels are below a 75 *I. Q.* than in the section whose mental levels are above 75. The feeble minded, quite in common with the rest of the population, have two kinds of intelligence—mental intelligence and social intelligence, the only difference being that the mental intelligence in the feeble minded is not on so high a level. It is the balance or imbalance, however, of these two intelligences in the individual that makes for social adjustment or social failure in all mental levels."

The Sex of Mentally Deficient Individuals.—BRIDGMAN (*Ment. Hyg.*, 1929, 13, 62) classifies according to the Binet scale 3675 individuals with *I. Q.*'s of less than 90 and analyzes them according to sex. She finds a preponderance of males in the idiot, borderline and dull normal groups while there is a preponderance of females in the imbecile and moron groups. She considers that these differences may be based to some extent upon variations in the type of delinquency and the type of supervision between the sexes. She states that these considerations do not, however, cover the discrepancies and feels that we must seek elsewhere for other factors. The construction of the test itself is possibly a factor in bringing out differences between the sexes. She analyzes the data on the basis of nationality and finds some variations here, the consideration of which leads her to the conclusion that the social element involved in the selection of cases to be brought to the clinic is probably the basis of discrepancies shown.

Mental Hygiene in the Public Schools.—WILE (*Ment. Hyg.*, 1929, 13, 70) would apply the principles of mental hygiene to every child in school. As education is a state problem and the normal school forms the point of departure for the training of teachers he would begin his program with an extension of the training-school courses to include training in mental hygiene together with courses familiarizing teachers with the educational and emotional reaction systems of children. There should also be courses in the interpretation of psychometric tests and education along the lines of the accepted modes of providing and developing remedial teaching. To produce any effective results he believes that mental hygiene clinics are necessary and should be provided by the state if not already available through some other source. He would

recognize the school system on the basis of an ungraded class to which all children entering the school would be admitted for the purpose of study and classification. Every child in this clearing class would have a careful physical examination upon entering. Psychologic tests and other special studies would be made while the child is in this class, prior to his assignment to any special group.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Fate of Colloidal Iron Administered Intravenously.—In this article POLSON (*J. Path. and Bact.*, 1928, 31, 445) presents a study of the distribution and fate of large doses of dialysed iron following intravenous administration to rabbits. The experiments were also used as an attempt to produce in rabbits a lesion similar to hemochromatosis in man. The animals were given large doses of iron and at varying intervals after the last dose they were killed and their organs examined histologically and chemically. The immediate effects depended upon the size of the dose and upon the rapidity with which it was administered. If any single dose was too large or given too quickly, the animal had convulsions, died, and on postmortem examination showed pulmonary embolism as the predominant picture. Where more prolonged study was followed, however, it became apparent that there were two principal results of the administration. These were: (1) Embolism, and (2) ingestion of iron by phagocytes derived from the liver, spleen and bone marrow. The greatest amount of iron in the lungs was as emboli in the vessels. No pulmonary infarction was noted and no iron was demonstrable in the bronchial epithelium. Phagocytosis was evident at the end of a week and was well advanced at the end of two weeks. The active cells were endothelials derived from the lung endothelium and large spheroidal cells, endothelial in type, of doubtful origin. The portal tracts were free from iron at all stages, but the Kupffer cells showed great avidity for the metal. These cells early became charged with iron. Subsequently, they became detached from the capillary walls and at the end of one week were seen in the lumina, later fusing into large multinuclear cells. While iron was evident in the Kupffer cells practically from the beginning of the experiments, it was only at the end of two weeks or more that it was found in the periphery of the liver lobules. A comparison of the lung and liver iron content was interesting, showing that in the shorter (three-day) experiments the ratio of lung iron to liver iron was 2.4 to 1. (After a single dose, the lung iron varied directly with the degree of embolism.) In

the longer experiments this ratio was reversed, the ratio at one week being 1 to 1, and at two weeks 1 to 2.1. It was thus apparent that by some unknown process the greater part of the lung iron ultimately reached the liver. The phagocytes of the spleen showed early avidity for the iron. These massed together and during the second week disintegrated, leaving iron depots in the splenic pulp. The Malpighian bodies were indifferent to the iron. Iron accumulated in the thoracic and abdominal lymph glands. Embolism of renal glomeruli was sometimes noted as an immediate effect. Iron did not appear in the tubules before two weeks, unless the tubules had been previously damaged. The iron content of the bone marrow rose toward the end of the second week. Iron was also noted in the cecum, in the epithelial cells of the mucosa and in the endothelial cells of the submucosa—facts which tend to verify the theory of at least partial excretion *via* the large bowel. In all other organs, iron was only found in the endothelial cells of the capillaries. Hemosiderosis was very readily produced. In even short experiments, the liver iron content was at least doubted.

Experimental Chronic Abscess of Lung.—Abscess of the lung has been produced experimentally by a number of investigators but it has been found more difficult to reproduce the chronic type comparable to the postoperative pulmonary abscess in man. HERMANN and CUTLER (*Proc. Soc. Exper. Biol. and Med.*, 1928, 26, 28) found that arterial emboli, infected with spirochetes, fusiform bacilli and other mouth microorganisms from a patient with pyorrhea alveolaris, when implanted in the pulmonary tissue produced chronic abscesses identical in most respects to those in man, namely, thick walled, lined with a dark gray necrotic membrane, of a foul odor and containing exclusively anaërobic bacteria. The same types of organisms introduced by way of the bronchi did not give this result. ADAMS, VAN ALLEN and DAY (*Proc. Soc. Exper. Biol. and Med.*, 1928, 26, 163) produced acute abscesses by emboli with *Staphylococcus aureus* which healed within four weeks but if ten days after the production of the embolic infection the lungs were insufflated with bronchiectatic sputum (which alone gave no abscesses), there resulted chronic abscesses. The latter authors, therefore, raise the question whether in man postoperative lung abscess which occurs from infected embolus may become superinoculated by mouth organisms through accidental insufflation and thereby assume the characteristics of bronchogenic abscesses.

Types of Tubercle Bacilli in Bone and Joint Tuberculosis.—The great importance of knowing more about the source of the tubercle bacilli in the extrapulmonary infections with tubercle bacilli makes this report by GRIFFITH (*J. Path. and Bact.*, 1928, 31, 875) particularly valuable. The summary of 5 series of cases from Great Britain showed that from tuberculous children under ten years of age with extrapulmonary infection the bovine type of bacillus was recovered in about 30 per cent, while this percentage was reduced to 8 in those over ten years and no bovine infection was found in any patient aged twenty-five years or over. The difficulties in determining the type, the distribution in various bones and joints, the question of the portal of entry and many other problems of tuberculosis are here authoritatively discussed.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Health Record of University Students as Related to Tonsillectomy.—FORSYTH (*Pub. Health Reps.*, 1929, 43, 560) made a study of approximately 1000 people, university students, with the idea of ascertaining whether the previous removal of tonsils materially affected the status of the individual with respect to health at the time of admission to the university and subsequently during his or her stay in the university. The group covered 703 individuals who had not had their tonsils removed, and 275 who had had their tonsils removed. There was little or no difference to be ascertained between the conditions in the two groups, although there was just a suggestion of some advantage in the group free of tonsils in general nutrition and general health grade. It was pointed out that the tonsillectomies must have been done on persons who were having some trouble and particularly subject to illness, and that the operations must have enabled that group to overcome the handicap and to enjoy health approximately equal to that of other students.

The Immunologic Relationship of Alastrim and Mild Smallpox.—LEAKE and FORCE (*Hyg. Lab. Bull.* No. 148, April, 1927) discuss briefly the literature on "alastrim" of Brazil and other parts of the world with special reference to its possible identity with smallpox. These officers detail their experiments, which were designed to show the immunologic relationship between "alastrim" as represented by strains from the West Indies and smallpox of the United States and vaccinia. The essential points of the summary are as follows: "A vesicopapular eruption was regularly produced in monkeys, through three generations, by inoculation with material, the sources of which were pustule contents, from three Jamaican patients with alastrim. Crusts from a Haitian patient with the same disease produced a similar eruption in two monkeys. Crusts from two American patients with mild smallpox (District of Columbia and West Virginia) produced similar eruptions in monkeys through three generations. Two monkeys successfully inoculated with alastrim were completely immune to vaccine virus thirteen and seventeen days later; the first of these was partially immune (gave a modified reaction or vaccinoid) to vaccine virus seventy-nine days after the alastrim inoculation. A monkey successfully vaccinated with vaccine virus was completely immune ten days later to alastrim and to smallpox inoculation. A monkey successfully inoculated with smallpox was com-

pletely immune twenty-two days later to alastrim and to smallpox. Another monkey successfully inoculated with smallpox was partially immune (gave a modified reaction or vaccinoid) to vaccine virus seventeen days later. Two monkeys successfully inoculated with alastrim were completely immune to another inoculation of alastrim thirteen and twenty-two days later, respectively, and the first of these was completely immune to a third inoculation of alastrim and an inoculation with smallpox eighty-four days after the first inoculation. Rabbits inoculated with alastrim showed some immunity to vaccine virus; those receiving two inoculations (directly with human material and with the first monkey generation) showed a higher degree of immunity than those inoculated once (with the second or third monkey generation). This immunity was not different from that shown by rabbits which had been inoculated with smallpox (second monkey generation). None of these rabbits showed marked lesions from their smallpox or alastrim inoculations. The fact that definite cross immunity exists between alastrim and mild smallpox and between alastrim and vaccine virus is additional evidence of the identity of alastrim and mild smallpox."

Malta Fever: A Problem for State and Municipal Laboratories.—HARDY (*Pub. Health Reps.*, 1929, 43, 503) points out that the previous work of Evans has shown a very close relationship between the organism of Malta fever and that of contagious abortion of cattle and surveys briefly the reports of Malta fever of bovine origin. In routine testing of the blood for typhoid fever it was made the rule to run also tests for Malta fever; during the time that the work was in progress 783 examinations were made which resulted in the disclosure of 41 cases of typhoid and 31 cases of Malta fever, which is held to indicate that in Iowa at least Malta fever presents a health problem comparable to that presented by typhoid. In the great majority of cases the physician had not suspected Malta fever and Hardy believes that in the past only the prolonged and severe cases have been studied while the milder cases and those of shorter duration have in general escaped detection. The technique of carrying out the reactions is given in detail.

Benzocain-Chaulmoogra Oil in Treatment of Leprosy.—JOHANSEN (*Pub. Health Reps.*, 1927, 42, 3005) notes that chaulmoogra oil has been used for a long period in the treatment of leprosy and calculates, therefore, that it has some virtue in the treatment of the disease. It is pointed out that oral administration is accompanied by disagreeable features and that introduction by the intramuscular route, either of the crude oil or of its refined products, is painful and ordinarily not well tolerated by lepers. The obvious disadvantages of intravenous administration are noted. An attempt was made to overcome the disadvantages of the intramuscular injection by adding to the oil 3 per cent of benzocain, together with 10 per cent of olive oil. The dose of this preparation was from 5 to 8 cc. although in a few cases almost double the latter amount was given. It was found that the oil was absorbed within forty-eight hours in most cases and rarely could any indication be found after three days. Of 24 cases 6 showed marked improvement, 12 showed moderate improvement, 5 showed slight improvement, and 1 was not improved. No claim is made that this treatment will cure leprosy; it was felt, however, that it is worthy of a further trial.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 18, 1929

Observation on the Differentiation of Bloodvessel Endothelium as Seen on the Yolk Sac in Living Fundulus Embryos.—E. R. CLARK and L. CLARK (from the Department of Anatomy, University of Pennsylvania). The method of study was similar to that used by Stockard,¹ namely, the observation of the living developing transparent egg of fundulus. The results agreed in all essential points with those of Stockard. Thus we saw the migration from the region of the embryo of cells which gradually showed the three-fold differentiation into orange chromatophores, black chromatophores and bloodvessel endothelium; also the localized differentiation of the erythroblasts and erythrocytes in a mass continuous with a mass in the posterior portion of the embryo proper. Moreover, we found that, over most of the yolk, and until circulation was established, the bloodvessel endothelium differentiates in the entire absence of erythroblasts and erythrocytes.

We were able to add the following points to Stockard's observations. The preendothelial cells, or "angioblasts," move out over the yolk as an anastomosing network of homogeneous, hyalin-appearing, mesenchyme-like cells. They may be seen as early as thirty hours. In the interstices cells of a slightly coarser type wander about, and (between the forty-fifth and fifty-fifth hour) develop either orange or black granules and become chromatophores, as described by Stockard. In addition are numerous small, round cells which move actively among the other cells, which divide frequently and rapidly, and which persist after the other types have differentiated, the ultimate fate of which has not yet been determined.

Through the period from forty to forty-six hours the angioblast cells continue to move actively over the yolk, increase by mitotic division and enlarge by the formation of longer processes which connect with neighboring angioblast cells. Rather suddenly, at about forty-six hours, there occurs a remarkable change in the angioblast cells, affecting enormous numbers over the extra-embryonic area simultaneously. The hyalin appearance gives way to a non-homogeneous condition brought about by the formation of holes or vacuoles in the interior and a fibrillar or lace-like net in the outer portions and in the processes. This phase is evidently one of intense activity, for cells which have undergone this loosening-up process change shape and position rapidly and are seen to undergo frequent mitoses.

The vacuoles enlarge and coalesce, and with the increase in the cavity thus formed is produced an anastomosing network of capillaries. Circulation of blood starts at about sixty hours.

This differentiation, occurring over a period of fourteen to fifteen hours, is not a steady progressive one in all cells. While the loosen-

¹ Am. Jour. of Anat., vol. 18, 1915.

ing up affects all angioblast cells, many revert to the homogenous phase. During at least two days after circulation starts there is continued formation of new vessels in the interstices of the first plexus, by the vacuolization of angioblast cells.

Throughout the process of angioblast migration, vacuolization and the formation of capillaries the angioblast cells remained specific and gave no indication of giving rise to erythrocytes or leukocytes.

Effect of Abdominal Thermal Applications on the Intraperitoneal Temperature.—S. BRILL (from the Laboratory of Research Surgery and the Department of Surgery, Division B, University of Pennsylvania). Thermal applications have been used extensively as therapeutic agents. Although there is no doubt as to their efficacy in the treatment of a variety of clinical conditions, there is some question as to how they act when applied to the treatment of intraabdominal lesions.

The effect of both heat and cold applications was studied on anesthetized and unanesthetized dogs, using the thermoelectric apparatus designed by Bazett and McGlone. Temperature readings were taken of the skin, subcutaneous tissue, deep tissue and peritoneal cavity. It was found that: (a) Cold applications had little effect on the intraperitoneal temperature, the greatest fall being 2.5°C ., which was observed in one instance; (b) hot applications in the form of a hot-water bottle over a towel, as usually used clinically, did not produce any appreciable changes; (c) an electric pad did not influence the intraperitoneal temperature of the normal animal to any great extent, but in an animal under anesthesia with a low rectal temperature it caused a rise of 3.5°C . intraperitoneally. Coincidentally, the rectal temperature rose 2.4°C .

These observations indicate that the beneficial effects of hot and cold abdominal applications are due to other causes than the effect on intraperitoneal temperature.

Bile Peritonitis and Bilous Ascites.—I. S. RAVDIN and M. E. MORRISON (from the Laboratory of Research Surgery, University of Pennsylvania). It is a well-established fact that the entrance of bile into the peritoneal cavity from a perforation in the extrahepatic biliary system will result in peritonitis if sufficient bile escapes. It is equally well established that the patient or animal may go for weeks or even months with large amounts of bile-stained fluid in the free peritoneal cavity without deleterious symptoms referable to the fluid itself. The clinician has frequently drawn no distinction between bile as such in the peritoneal cavity and the bile-stained fluid often found when portal stagnation and ductal obstruction are present. Contrary to the view of many surgeons, the authors have confirmed previous investigations that non-infected bile will cause bile peritonitis.

It was found that the bile-salt content of bilous ascitic fluid was extremely low when compared with the bile-salt content of fistula or gall-bladder bile. In the cases having innocuous bile-stained fluid in the peritoneal cavity in association with obstruction of the common duct, it is likely that this is the result of portal stagnation and transudation from the portal system. The low bile-salt content of the ascitic fluid can be explained by the observations of other investigators who

have found that after complete hepatic secretory suppression the bile-salt content of the blood returns to normal or subnormal values.

After concentration of the bilous ascitic fluid to a point where the bile salts were present in lethal doses, intraperitoneal injections killed mice in approximately the same period of time as equal concentrations of pure bile salts or of bile salts in gall-bladder or fistula bile. In a dog weighing 11 kilos, from which 150 cc. of bile-stained fluid was removed from the peritoneal cavity, the total bile-salt content was 0.255 gm. The amount of bile salts necessary to kill the animal within twenty-four hours would have been approximately 6.05 gm. (the amount of bile salts in 55 cc. of whole gall-bladder bile). The large amount of bile salts found in bile escaping from the extrahepatic ductal system will explain bile peritonitis, while the very low concentration found in the bilous ascitic fluid makes these accumulations apparently innocuous.

Anesthesia and Cell Division in Sea-urchin Eggs.—R. BLUMENTHAL (from the Zoological Laboratory, University of Pennsylvania). One of the chief criteria of anesthesia has been the reversible inhibition of cell division. The present experiments, however, show that anesthetics do not always prevent cell division. Fertilized *arbacia* eggs exposed to sea-water solutions of KCN, methyl, *i*-amyl, *n*-propyl and *i*-propyl alcohols in anesthetic concentrations will undergo cell division if the eggs are placed in these solutions within the ten minutes preceding the time when cell division is due. If the eggs cleave once and are permitted to remain in the anesthetics no further cleavage takes place.

It is suggested that cyanids act by preventing oxygen-protoplasm unions within the cell, although they do not prevent the utilization of the oxygen already in combination in the cell. As soon as this latter oxygen is used up, and since no further oxygen becomes available, development within the cell ceases.

Correction: On page 358 (March, 1929), under Chart III of Dr. Margolis' article on Chronic Pentosuria and Migraine the statement which reads "10.3 per cent pentose for February 21" should read "0.3 per cent pentose for February 21."

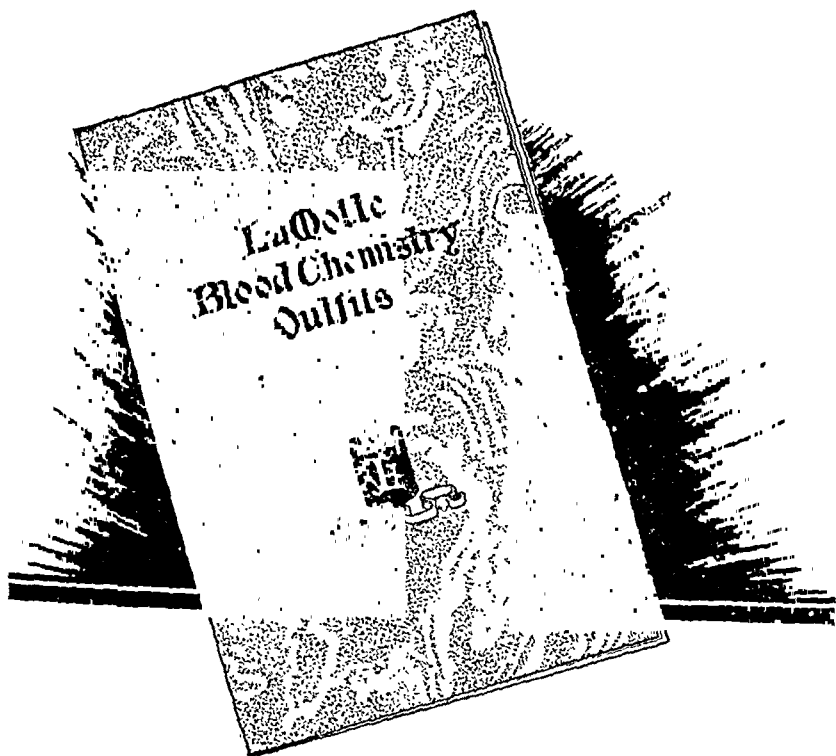
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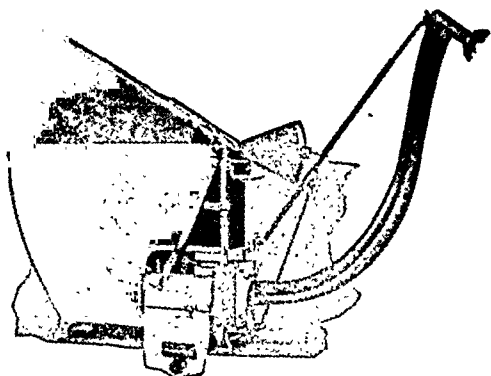
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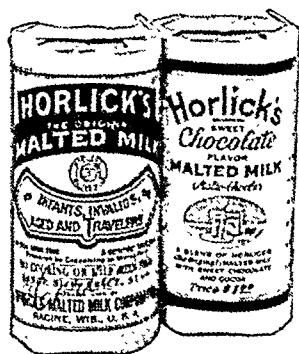


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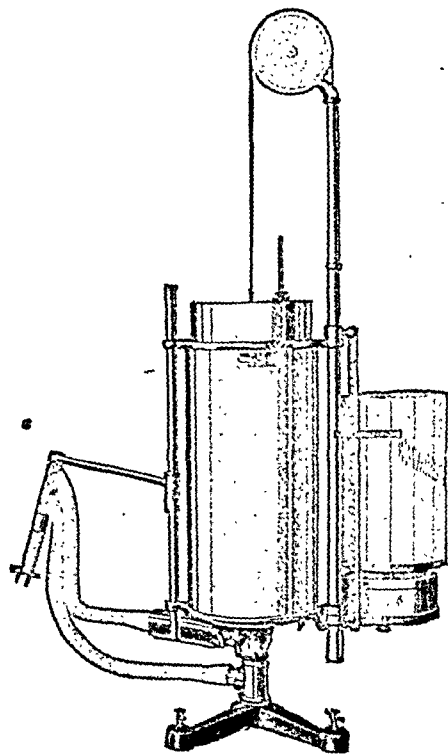
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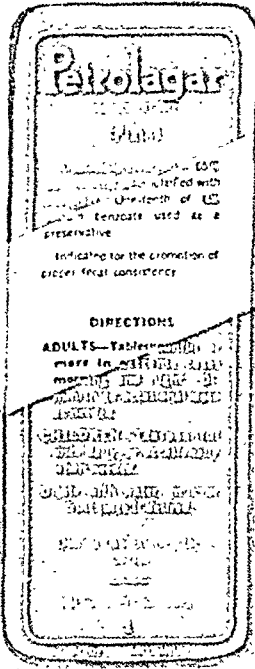
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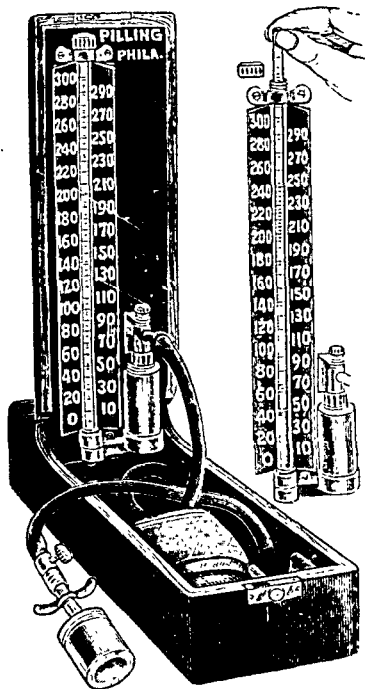
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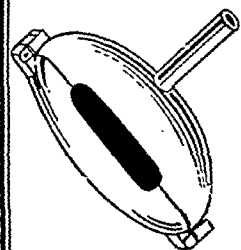
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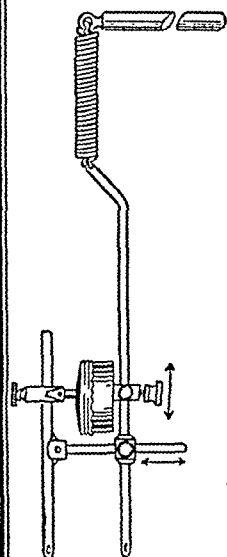
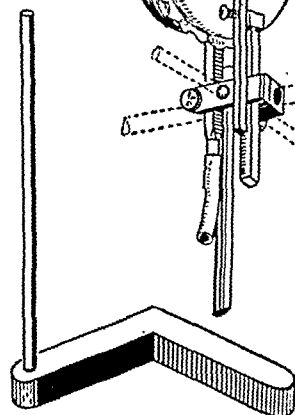
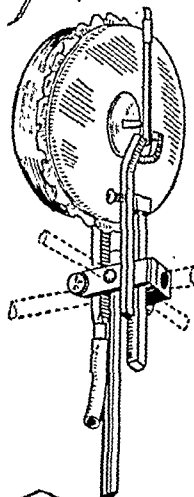
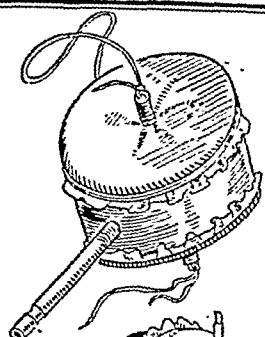
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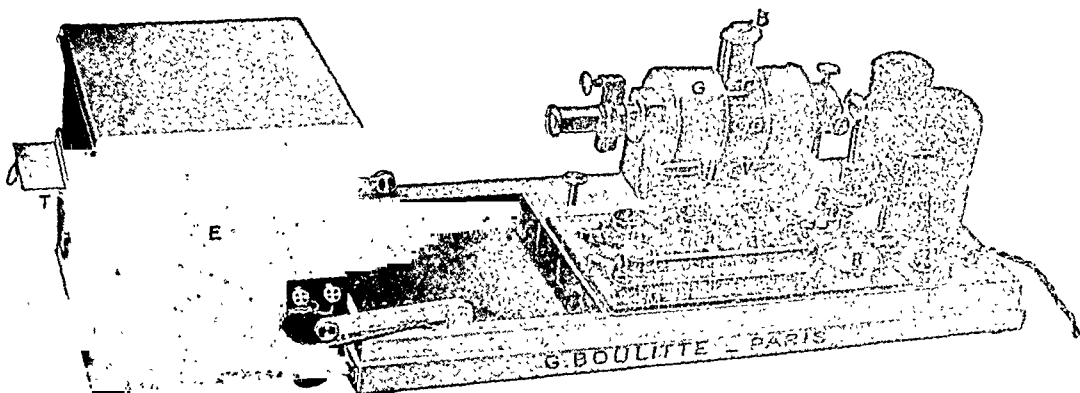
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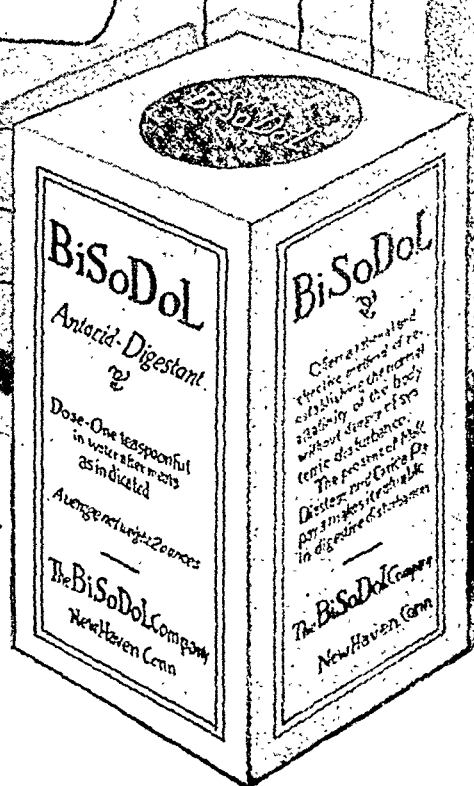
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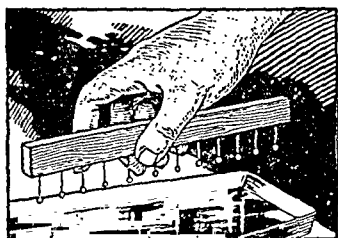
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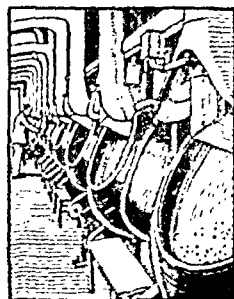
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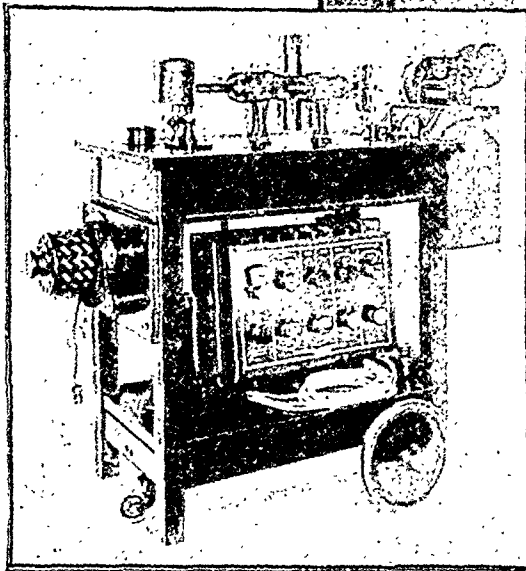
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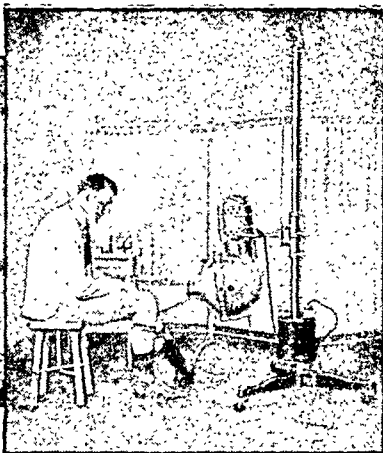
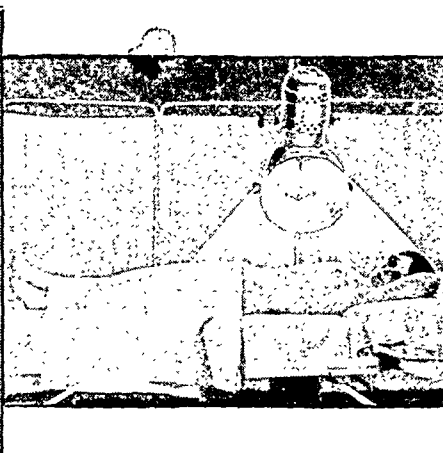
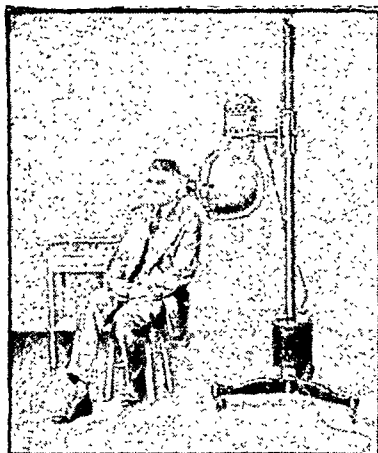
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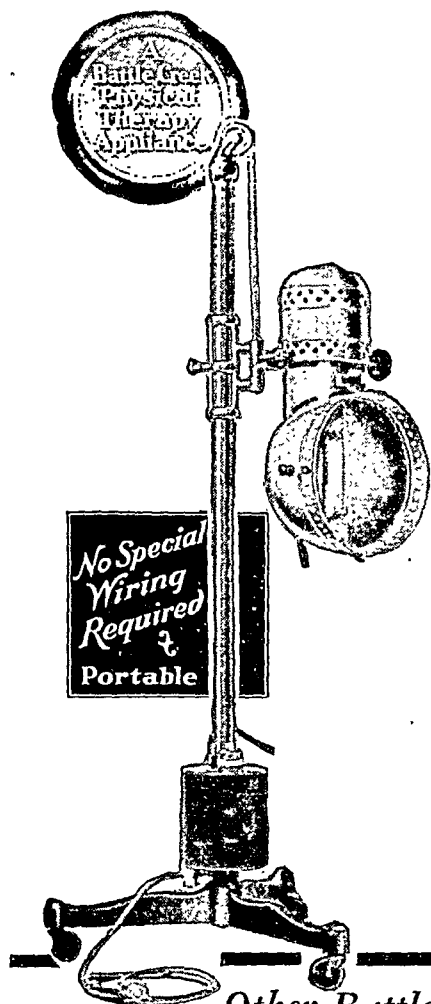


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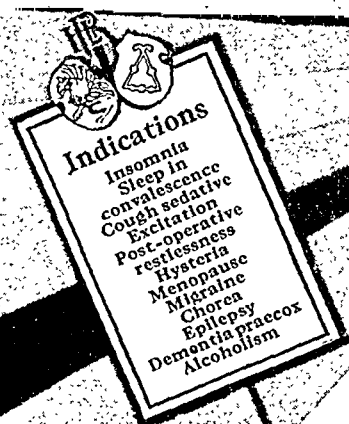
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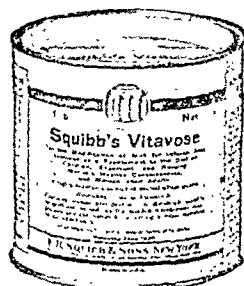
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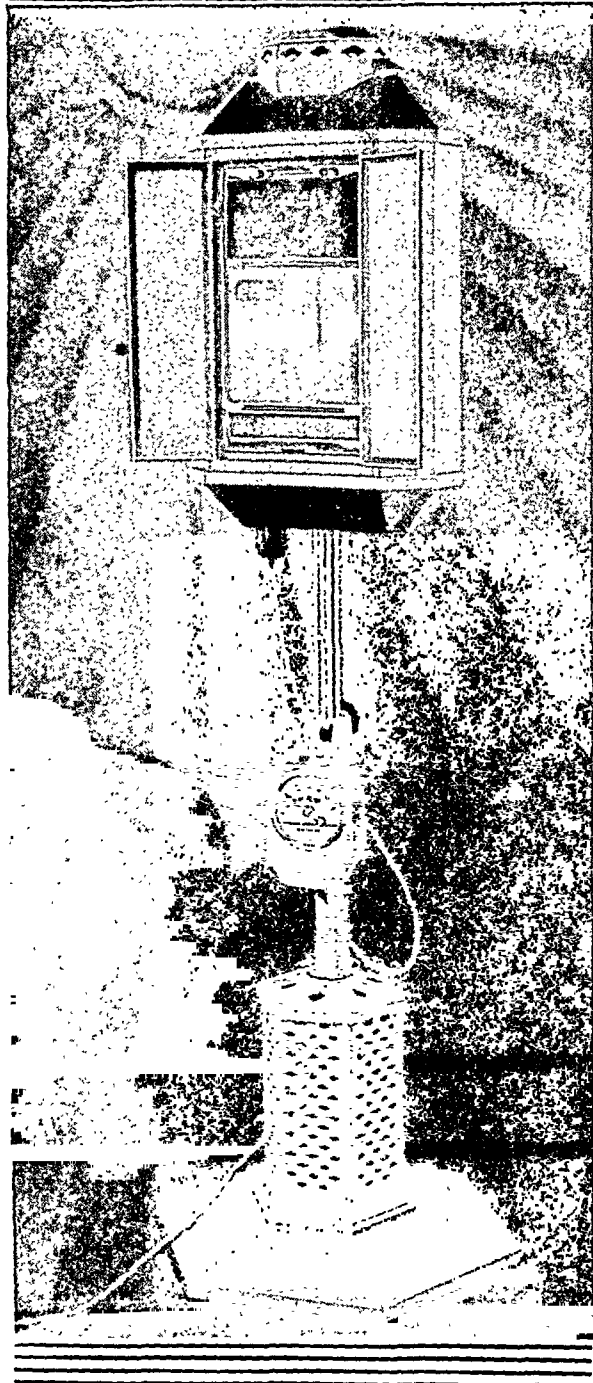
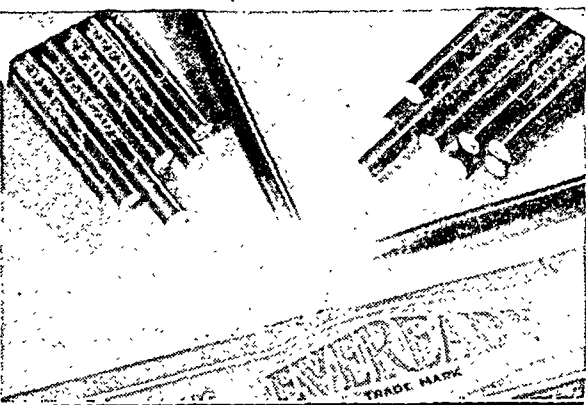
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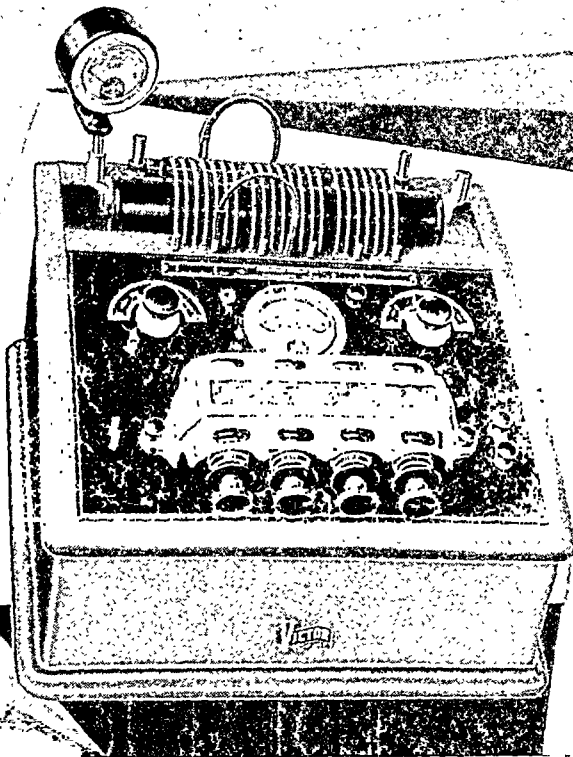
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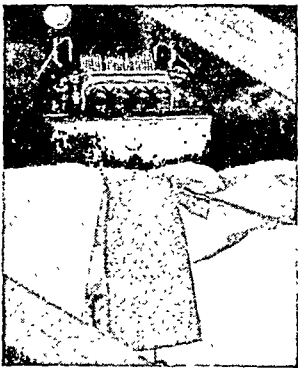
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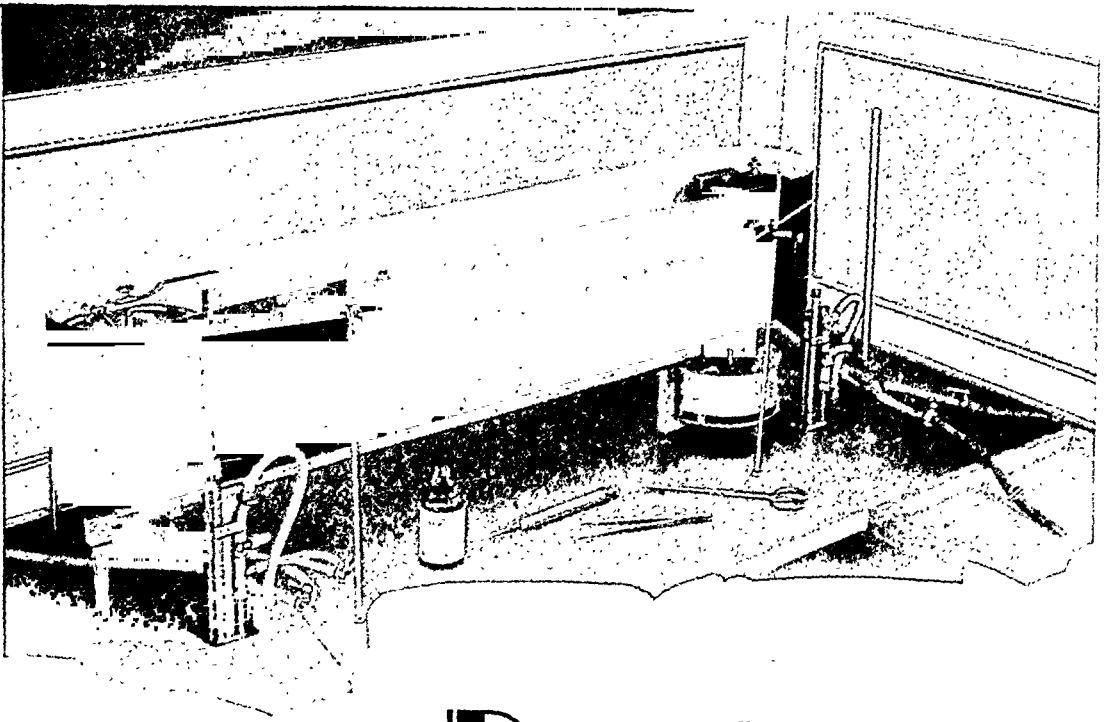
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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MAY, 1929

ORIGINAL ARTICLES.

THE PROBLEM OF PIGMENT FORMATION.*

BY BRUNO BLOCH, M.D.,

PROFESSOR OF DERMATOLOGY AND VENEREAL DISEASES AT THE UNIVERSITY OF ZURICH,
ZURICH, SWITZERLAND.

As the subject of my lecture this evening I have chosen the problem of pigment formation, which I believe to be not only of dermatologic but of general interest. The particular pigment of which I wish to speak is called melanin and is an organic dye, which is found in all animals, from the lowest to the highest.

Pigment, its formation and function, plays an important rôle in every branch of biologic science. As a matter of fact, we encounter this problem in comparative zoölogy, biology, biochemistry, anthropology, physiology and pathology, and above all in dermatology.

I need only to remind you of the importance of the color of the skin and hair in the classification of the human races and its importance in human pathology, particularly in various endocrine changes, as, for instance Graves' disease, Addison's disease, pregnancy and scleroderma. Moreover, I wish to remind you that the most malignant growths are melanotic tumors, and that both the diagnosis and therapy of this condition are impossible without an exact consideration of the pigmentary changes.

The entire problem of pigment formation is extremely difficult and complicated and far from its complete solution. It is a morphological as well as a chemical problem, and no one who does not master both these factors can hope to approach it with success. It has, moreover, an entirely different aspect in the cold-blooded animals than in the higher ones. This difference lies in the morphology, the genesis and especially in the function of the pigment.

* Read before the Harvard Medical School, April, 1928.

Here it has a vital importance in temperature regulation, in mimicry and protective coloring, and the pigment cells themselves are provided with nerves and are capable of contraction and expansion. These faculties have degenerated to a great degree in higher animals. In these latter we can no longer speak of a vital function of pigment.

Before discussing the main problem I must give a definition of certain terms. We call *melanoblasts* those cells which are capable of forming pigment, while those which contain pigment which they themselves have not elaborated, but have only obtained elsewhere (absorbed or phagocytized) are called *chromatophores* or *melanophores*.

The Distribution and Localization of Melanin in Higher Animals. If we do not take into consideration the unimportant occurrence of melanin in certain parts of the nervous system, the melanin in higher animals is found only in two organs, which could, therefore, be designated "pigment organs." These are the eye and the skin.

In the eye we find pigment in the pigment layer of the retina. This pigment is ectodermal in origin. On the other hand, the pigment in the ciliary body and the choroid is of mesodermal origin. We have, therefore, in this organ ectodermal and mesodermal melanoblasts.

The human skin contains pigment in its ectodermal and mesodermal parts.

The ectodermal pigment of the skin and also of the mucous membranes is found in the epidermis (or epithelium), particularly in the basal cells, in the hair matrix and in the cells of the pigmented naevi, which develop through a metaplastic process from the epidermal cells.

All these cells form the pigment that they contain in their protoplasm; they are, therefore, melanoblasts of ectodermal origin.

The mesodermal part of the skin, the corium, contains in man and in certain higher mammals two entirely different kinds of pigmented cells.

One type is found regularly but in very varying numbers in the papillae and also in the deeper layers. They are plump, sometimes somewhat branched cells of very variable form containing coarse granules of pigment. These are the chromatophores of the human cutis. As my assistant, Miescher, and I have shown, they do not form their pigment themselves. They are connective-tissue cells which have phagocytized pigment, which was originally formed in the epidermis. In some pathologic hyperpigmentations of the skin these chromatophores play a definite rôle, as, for instance, in tar, arsenic and Roentgen ray melanoses and so forth.

My collaborator, Sulzberger, recently described a previously unknown pathologic condition, in which there were curiously shaped, widely disseminated pigmented spots on the skin, which histologically consisted merely of very large heaps of such chromatophores (*incontinentia pigmenti*).

Another type of pigmented cells found in the cutis differs entirely in form, localization and nature from the above-described chromatophores. They are mesodermal melanoblasts, which I named *Mongolen-Zellen*. These cells lie for the greater part deep in the corium and are generally long and ribbon-like; they elaborate their own pigment, entirely independently of the epidermal pigmentation and embryologically long before this latter has appeared.

In certain animals this type of pigment is of much greater importance than the epidermal pigmentary system. For example, in the Japanese negro fowl these cells permeate not only the entire connective tissue, but also the internal organs, the ovaries and even the heart.

If you look at certain monkeys (*macacus*) you will see that some parts of the skin are colored a bluish gray. This color is also due to the presence of these mesodermal melanoblasts, which lie in the depths and shine through the transparent and unpigmented epidermis.

Analogous spots with the same color are found in all Japanese or Mongolian newly born, particularly in the sacral region. Attention was first called to this fact by the German, Baelz, and interpreted as pointing to a closer relationship of the Mongolian race to the apes. This worried the proud Japanese race, and there was great rejoicing in Japan when somewhat over twenty-five years ago the Japanese, Fujisawa, succeeded in the Munich Policlinic in demonstrating for the first time such a Mongolian spot in an infant of European origin. Since this time we have learned that such Mongolian spots can and do occur in the newly born of all races, but investigation with dopa and silver reactions first showed me that the microscopic elements, which constitute that which is macroscopically the Mongolian spot, are present in each and every embryo and newly born infant. We must, therefore, admit that the Japanese were right, insofar as the differences in the races are only quantitative ones. The occurrence of these cells seems to me to be one of the best proofs of the descent of man from the ape, or a common ancestor.

There is a second condition in which mesodermal melanoblasts are found in human beings. This is in the so-called blue *nævi*, which were first described by Jadassohn. These are large or small circumscribed moles, which differ from ordinary brown moles in their blue color. Microscopically they consist mainly of pigment cells, which are identical in every respect with the cells of Mongolian spots. Their blue color is caused by the same physical phenomena.

I once examined a number of Hindus and found numerous blue *nævi*. An extremely exceptional case is represented by this wax model. It is the case of a Swiss child, whose skin presented no less than 42 blue *nævi*, besides several brown ones.

As the cells of these blue *nævi* are mesodermal melanoblasts, the malignant growths which originate from these moles are, therefore,

true melanosarcomas. Such tumors were described for the first time by Darier. When one calls the melanotic tumors which originate from the ordinary brown *nævi*, melanosarcomas, as is so frequently done, it is an error from the viewpoint of their genesis. These, as I have shown, originate from ectodermal melanoblasts and are, therefore, *melanocarcinomas*.

The Characteristics and Composition of Melanin. In the foregoing, I have outlined the occurrence and distribution of pigmented cells. I come now to the most essential part of our problem, and the following points now interest us: Where is this brown dye formed? What is the mechanism of its formation? From what mother substance (melanogens) is it elaborated? What is its constitution and what is its significance and function under normal and pathologic conditions?

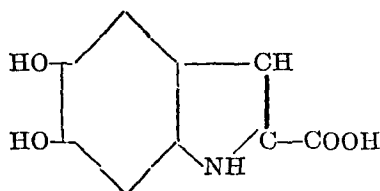
Lack of time only permits me to discuss briefly the above questions.

At first glance the method of determining the characteristics and composition of *melanin* seems simple and self-evident. It appears only necessary to extract the melanin from the organs, which contain it in great quantities (hair, skin, eyes) and to isolate and analyze it. This method has been tried a great number of times and has never led to satisfactory results. Upon closer inspection, the reasons for this are clear. It is absolutely impossible to isolate an organic substance which is so complicated and which cannot be crystallized, from the even more complicated milieu, represented by the pigmented tissues.

The data given by the different authors, among whom are many well-known biochemists, differ so greatly that they clearly demonstrate the fallibility of the method. These difficulties of the classical chemical method are shown by the fact that even the results of the analysis of melanins which have been artificially elaborated from known definite substances, such as tyrosin or dioxyphenylalanin, vary greatly. We find, for instance, that the nitrogen content varies from 4.3 to 8.5 per cent. But in spite of these facts, the investigations have given some information and I will, therefore, summarize the results, which seem to me the most important:

Melanin is an organic high-molecular dyestuff or pigment. It is amorphous, even upon Roentgen spectroscopic examination. It is insoluble in water and in organic solvents; it is a negative colloid, going into colloid dispersion in alkaline media. Natural melanin surely contains carbon, nitrogen, hydrogen and oxygen. The iron and, according to recent investigations by Dr. Schaaf from my laboratory, also the sulphur which have been found are impurities coming from the organs from which the melanin has been extracted (keratin). Schaaf and I have shown that the nitrogen is not amino nitrogen (not demonstrable by Van Slyke). According to Raper, the nitrogen in tyrosin melanin, which is formed artificially by the

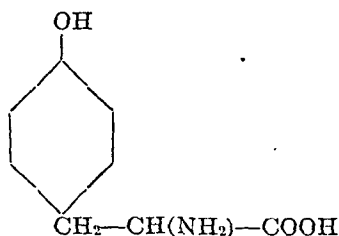
action of tyrosinase on tyrosin, is in an indol ring. As a matter of fact, under those experimental conditions he could isolate a 5-6 dihydroxyindol-2-carboxylic acid:



This fact explains why the melanin gives the pyrrol reaction. All melanins are capable of reducing certain metallic salts, particularly silver nitrate. This silver reaction is of great value because it enables us to make visible the smallest traces of melanins and perhaps even certain premelanins in sections of pigmented tissues.

The Formation of Melanin by the Action of Oxydizing Ferments. Since the ordinary chemical methods did not lead to satisfactory results, the problem had to be approached from a different angle, which we define as the biochemical instead of the purely chemical viewpoint.

Various authors, particularly Bertrand and Chodat, showed quite some time ago that certain plants possess oxidizing ferments capable of producing melanins from colorless organic cyclic complexes—melanogens—as, for instance, phenol, pyrogallol and tyrosin. Among these ferments, tyrosinase is particularly important. It is found in potatoes, mushrooms and other vegetable tissues. This ferment is specific and elaborates a melanin from tyrosin.



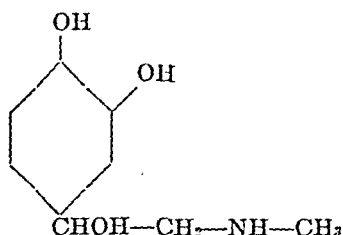
The chemical process of the formation of tyrosin melanin has been carefully studied by different authors, but Raper's recent work was the first to throw more light on the question. He showed that in the formation of tyrosin melanin dioxyphenylalanin was formed as the first intermediate product. Further products were the above-mentioned indol bodies.

Fürth was the first to conceive the idea that the formation of animal melanin also may be the result of a similar process. Even prior to this Biedermann found tyrosinase in meal worms. Fürth found tyrosinase in the hemolymph of butterflies, Pzribram in the ink glands of cephalopods and in the integument of certain cold-blooded animals.

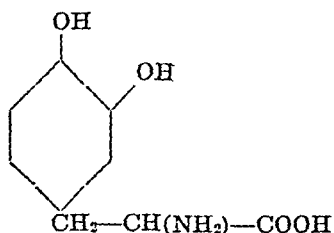
My own investigations have led me to believe that in higher

animals, particularly in mammals and man, the melanin is formed by a special ferment, the dopa-oxydase.

The Dopa Reaction and its Results (the Formation of Melanin by the Dopa-oxydase). My investigations were originally based on Addison's disease. In this disease we can observe one of the strongest hyperpigmentations of the skin combined with a lesion of an organ whose main product is a pyrocatechin derivate, *adrenalin*.



For this reason I experimented with the cyclic amino acid which is most closely related to adrenalin, that is, 3-4 dioxypyphenylalanin, which for the sake of convenience I call *dopa*.



Technique. Frozen sections are placed in a 1 per cent solution of dopa for about twenty-four hours at room temperature under the conditions which I have enumerated in my article in the handbuch, (see literature) the most important of which is the adjustment of the H-ion concentration. They are then mounted as usual.

The Principle of the Method. The pigment forming ferment, the so-called dopa-oxydase is capable of converting the colorless dopa to a dark insoluble melanin, the dopamelanin. All cells which contain this ferment are darkened by this dopamelanin, as soon as they are brought in contact with the dopa. This darkening is proportional to the quantity and activity of this ferment.

The dopa method has the great advantage of enabling us to study the exact site of pigment formation. It enables us, for instance, to observe the form of the melanoblasts and to demonstrate that pigment is formed only in their protoplasm and not in the nucleus. It also permits us to distinguish melanoblasts from chromatophores.

I may add, moreover, that it is possible to demonstrate the oxydase in extracts of the pigmented skin of newborn rabbits.

The Results of the Dopa Reaction. Following are the results of a more general nature:

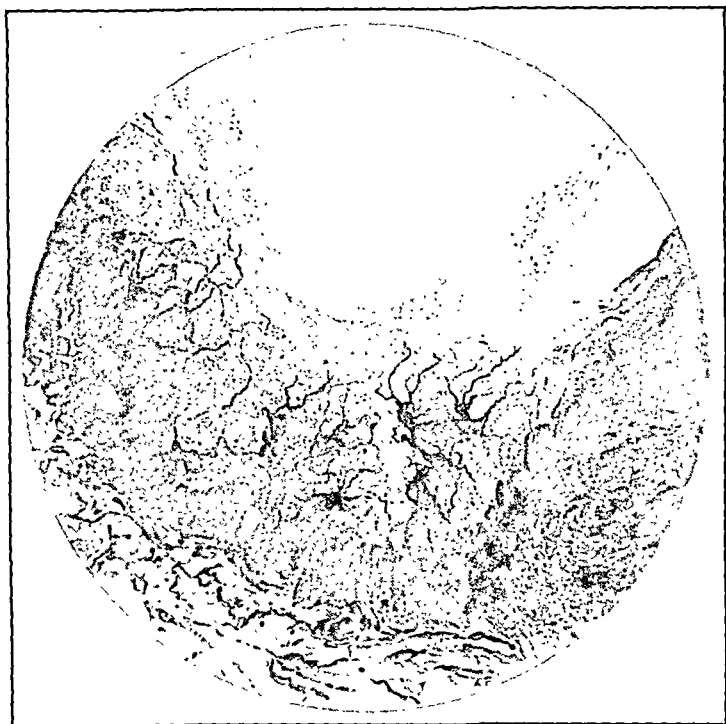


FIG. 1.—*Cells of Langerhans* (nerve elements) in the epidermis demonstrated through a gold method.

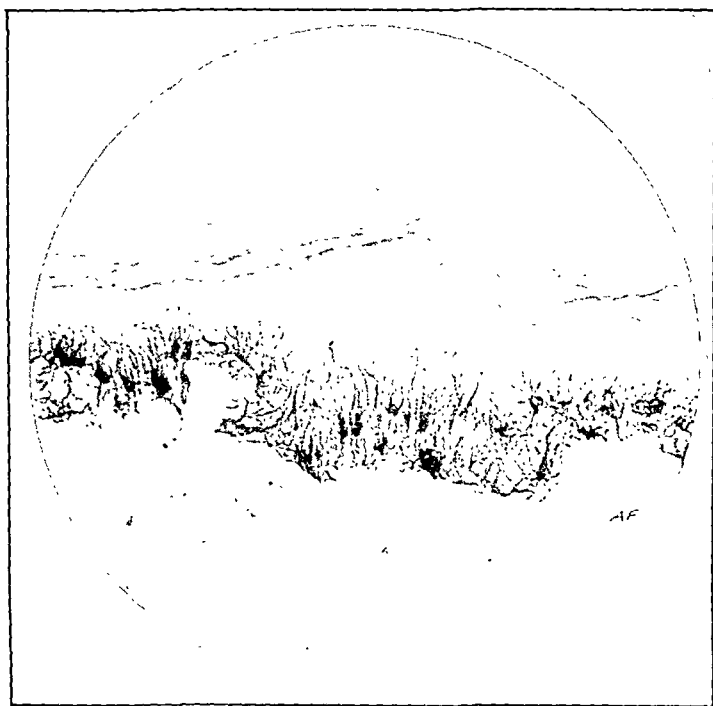


FIG. 2.—*Dopa reaction* in human skin ten days after application of *Thorium-X*. Transformation of basal into *Dendritic cells*.



FIG. 3.—Dopa reaction in *Melanocarcinoma* originating in the skin.



FIG. 4.—*Blue Nævus*. Dopa reaction. The reaction is positive in both basal cells of the pigmented epidermis as well as in the mesodermal melanoblasts (cells of blue nævus).

1. Under certain definite conditions, which I have given in detail in my work on this subject, the reaction is specific. No other substance, such as, for instance, pyrrol, tryptophan, not even tyrosin or adrenalin give the reaction. The slightest change in the dopa molecule is sufficient to make the reaction negative.

2. The reaction is of fermentative nature and satisfies the requirements necessary for such a supposition as I have shown in my experiments.

3. The reaction is only positive in the protoplasm—never in the nucleus. That is one of the strongest proofs against the theory that the nucleus takes part in the pigment formation.

4. *Dendritic Cells.* The dopa reaction, moreover, brings to light an extraordinarily interesting biologic phenomenon through a morphologic picture. It shows that melanoblasts very often possess numerous branching processes—hence the name dendritic cells. These curious dendritic cells have been known for many years, in lower as well as in higher animals. They can be observed under certain conditions in native sections and even better through the use of the silver method. Becker, of Chicago, in investigations undertaken in my clinic, has shown that they are more widely distributed than hitherto supposed, both in the human skin and in the mucous membranes of ectodermal origin.

But it was the dopa reaction which first showed how very frequently pigment-forming cells have this form and that there are cases in which practically each and every basal cell has dendrites. This was demonstrated, for instance, by my assistant, Peck, in studies of pigment formation in human epidermis after exposure to thorium-X.

The biologic significance and the genesis of these pigmented dendritic cells is a special problem in itself which until now has not been quite satisfactorily solved. In my opinion, they are melanoblasts in an active stage of pigment formation.

At any rate it is absolutely wrong to identify them with the Langerhans cells, as has been frequently done, for instance, by Pautrier and Masson. The true Langerhans cells which can be best demonstrated by gold methods have nothing to do with pigment formation. They are nervous elements, parts of the highly differentiated nervous system of the epidermis.

I think it would interest you to see some pictures of these elements which I have made by my modification of the gold method, in some as yet unpublished studies on this subject. This may give you an idea for the first time of what the nervous system in the epidermis really means. (Fig. 1.)

We will now undertake to answer the following important questions:

Where, when and under what conditions is the dopa reaction positive?

In all places in which we must assume that an autochthonic formation of pigment takes place the reaction is positive. It goes absolutely parallel with the formation of pigment in regard to time, place and intensity; there, where there has never been formation of pigment, or where this has ceased, the specific reaction is always negative.

Some Concrete Examples of the Results Obtained with Dopa Reaction

(a) *In the Eye.* As I have stated above, the pigment of the eye is formed early in the embryonic period, as well in the ectodermal retina as in the mesodermal choroidea. As was shown by my collaborator, Miescher, in a very painstaking and technically difficult investigation, the dopa reaction is positive in both and, which is more significant, exactly and only during the period of pigment formation (during the fetal life). Indeed, for instance, in the case of the chicken embryo, the pigment formation in the retina begins on the third day, reaches its maximum on the seventh and ceases on the eighteenth day. In the choroidea it begins only on the fifteenth day. Only at that particular time the dopa reaction is positive.

At first glance it may seem peculiar that pigment formation in the eye takes place only during a short time in the embryonic stage. When we consider the matter more closely, however, we see that this must be so on account of the function of the eye which would be impaired if the pigment formation was as easily influenced by outside factors, as is the case in the skin. As far as we know, there is only one condition in which the rule is broken. This occurs when malignant pigmented tumors (melanocarcinomas or melanosarcomas) arise from the pigmented parts of the eye. In this case the latent pigment function and parallel with it the positive dopa reaction reawaken.

(b) *In the Skin.* In the ectodermal parts of the skin and the mucous membranes the dopa reaction is positive in all cells which are capable of producing pigment, namely, in the cells of the basal layer of the epidermis and follicles and in the matrix of pigmented hairs. In all places one can here again observe the absolute parallelism between the first appearance of pigment granules on the one hand and the positive dopa reaction on the other. In the hair of the human embryo the first traces of pigment are found about the fourth to the fifth month. At this time and in the same places the first melanoblasts with positive dopa reaction are to be found. Only much later, at about the time of birth, do we see pigment formation concomitant with a positive dopa reaction in the basal layer of the epidermis, probably under the influence of light.

It is well known that graying of hair (canities) is a usual accompaniment of old age. The causes for this more or less physiologic fact have been investigated in vain by many scientists, among them the

great Metchnikoff. In the light of my theory, the process becomes clear. The matrix of the white hair does not give a dopa reaction. It has lost its pigment-forming oxidizing ferment, the dopa oxydase, with a resulting pigment-free or white hair.

If we make a section through the skin of a guinea pig, which is partly colored and partly white, the dopa reaction is positive only in the matrix of the colored hairs and always negative in the case of the white ones. A similar fact is to be observed in the case of vitiligo in man; there where the skin has become definitely pigment-free, the reaction is negative, whereas in the surrounding skin the reaction is positive and often increased in the hyperpigmented ring.

One of the most effective causes of skin hyperpigmentation is, as is universally known, the exposure of the skin to rays such as ultra-violet, Roentgen rays, thorium-X, etc. Under no other conditions, do we find such strong dopa reactions and so many and such beautiful dendritic cells as in such rayed skin. In the microscopic demonstrations, I wish to draw your attention to the sections showing a dopa reaction in a skin which has been exposed to thorium-X.

The dopa reaction is furthermore positive in the cells of pigmented brown moles—just as it must be according to the theory—and naturally also positive in the malignant tumors which arise from them, the melanocarcinomas. This applies not only to the primary tumors, but even to far distant metastases.

As I have said in the first part of my lecture, in the mesodermal part of the skin, in the corion, we must distinguish two entirely different sorts of pigmented cells—the chromatophores, which are nothing but pigment phagocytizing connective-tissue cells, and the pigmented cells of the Mongolian spots, the blue nævus, etc., which elaborate their pigment themselves. If the theory is correct, the dopa reaction must be negative in the chromatophores and positive in the Mongolian cells. That this is so, you can plainly see from the histologic pictures which I am showing you.

The curious pigment cells of the Japanese negro fowl, the gray mouse, the apes, the Mongolian spots and the blue nævi, which we have learned to know, are, therefore, actually mesodermal melanoblasts, and tumors arising from the blue nævi are melanosarcomas.

I need scarcely remark that a tremendous number of other problems in this field are still awaiting solution.

Of these, I only want to touch on the one concerning the nature and origin of natural melanogens.

As I have emphasized, the dopa reaction is an indicator of the presence of the pigment-forming oxydase. But this fact does not necessarily mean that dopa is the actual mother substance of natural melanin. However, there are some indications which suggest that pyrocatechin derivatives may play a rôle as substrates in the formation of natural pigment. I have already mentioned two points: the specificity of the dopa reaction and the occurrence of

dioxyphenylalanine in formation of melanin by the tyrosinase-tyrosine reaction.

I want to draw your attention to a third and very interesting fact which is generally ignored. The only physiologic pyrocatechin derivative is, as far as we know, adrenalin.* Under pathologic conditions, except in one particular case, pyrocatechin derivatives play no rôle. As Salkowsky, Tannhauser and I have found, such substances can occasionally be demonstrated in the urine of patients with general melanocarcinomatosis, melanemia and melanuria. This cannot be mere coincidence. It is logical to assume that these pyrocatechin derivatives come from the mother substances of melanin which must, of course, be formed in great amounts in such cases, become free through the disintegration of the tumor cells, get into the blood and are eliminated through the kidneys.

From all the facts, which I have now elucidated, I believe myself justified in drawing the following conclusion, which contains the gist of my researches on pigment formation by means of the method of the dopa reaction:

Conclusion. The specific dopa reaction is positive in higher vertebrates in all places where melanotic pigment is formed, that is, in the cells which are capable of producing pigment, the melanoblasts. A close parallelism exists between natural spontaneous pigment formation and the result of the reaction, as regards time, place and intensity. It is this parallelism which logically points to an innate connection between both phenomena. Wherever the natural formation of pigment is going on, the reaction is positive, and where pigment formation is temporarily or definitely lacking, the reaction is negative. Thus the dopa reaction must be an indicator of the existence of the faculty of natural melanin production (however not of the presence of melanin itself).

The agent within the cells, which is responsible for the dopa reaction, has the characteristics of an oxidizing ferment. We conclude that this oxidizing ferment which is demonstrated by the specific dopa reaction, is identical with the natural pigment producing oxydase and therefore call the latter dopa oxydase.

The nature of the mother substances of natural melanins (melanogens) is not yet known exactly. However, certain facts may indicate that pyrocatechin derivatives play a rôle in the process of the formation of natural pigment.

I hope that I have been able to show in this short lecture that modern dermatology does not limit itself to a small field only but includes interesting biologic problems of great general importance.*

* For complete details as well as bibliography, I refer the reader to my publication: *Das Pigment, Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Springer, 1927, vol. 1.

NOTE.—I wish to express my thanks to my assistant, Dr. M. Sulzberger, for his great help in the translation of this paper.

THE AGING OF THE HEART MUSCLE REGARDED FROM A GENERAL BIOLOGIC POINT OF VIEW.*

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Introduction. In any current discussion of the subject of diseases both in and of old age, an effort must be made to define accurately first what is meant by growth and second what is meant by disease. Without making this effort it is unlikely that satisfactory ideas of the nature of this matter can be attained. I think it is probable that an enquiry in this special form is new.¹ To physicians, the question assumed significance because of certain occurrences; it became apparent² several years ago that a time had arrived when great numbers of people were no longer dying of acute infectious diseases and that the days of those who were saved were being terminated by quite other processes. For this reason, the importance of the conditions in which old age is spent and the diseases to which it is subject appear to require more exact examination and analysis. The reflections which were entertained concerning the change were far from precise as can readily be appreciated now, when it is recalled that to meet the new issue Societies for the Prevention and Relief of Heart Disease were created. There can be little doubt that the nature of the problem with which these societies intended to deal was inadequately understood. It was known but, as Sir James Mackenzie would have said, it was not appreciated what were the varieties of the disease which were involved. This has been found a point of importance because, as is now known, susceptibility to given diseases varies with age. Nor was it known what number of individuals was afflicted by each one of them. There would, it seems certain, had these matters been clear, have been less emphasis on prevention and relief and more no doubt on reflection, on analysis and on investigation concerning what actually was the new situation.

General Considerations. In a sense, the subject I mean to discuss is not new. Speculation on the natural history of man, his origin, growth and destiny is so ancient, that it precedes even the systematic writings of Aristotle. But it is necessary first of all to become convinced that this subject involves considering both the state and the diseases in and of old age, and is, as I believe it should be, a matter of natural history. Clearly, beginning perhaps with the Psalmist, there has been a popular natural history. In recent years, a recrui-

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descence of interest in precisely this matter has developed; many men have supposed that there was something arbitrary in the selection of the Biblical term of seventy years, that there was in all probability something that might be altered to prolong this gift of life, if not indefinitely, at least beyond the conventionally accepted term. Whether there is justification in this view is open to debate but better still to investigation. Confidence in the belief, that the duration of the accepted span was not so firmly fixed as was commonly believed, was stimulated by a number of occurrences. It was obvious that actuarial analysis was making it appear that expectancy at birth of the duration of life was undergoing change. In Massachusetts, after a lapse of fifteen years, life appeared to have lengthened 30 odd per cent. Elsewhere similar phenomena were observed. That this alteration was related to the gradual disappearance of infectious diseases in the earlier years was not at once apparent; nor did one appreciate the fact that expectation of life in the later decades had not increased. During these later years also the extraordinarily interesting demonstration by Carrel that tissues when explanted from metazoa could under appropriate conditions be maintained alive in subcultures indefinitely, just as could bacteria, yielded the impression that the gift of immortality had been bestowed on them, and came not only as a great surprise but led many speculators to infer that what is possible in their case might be possible also in that of the whole complex organism. But the step from these conceptions to those having in view an adequate, not to say complete, understanding of the life processes of man and of the accidents and diseases to which he is subject is great. What these processes actually are and how they may be described seems, and without doubt is, a long and tedious labor. But to be in possession of the knowledge which can be gained only in this way is in all probability essential, certainly to understand and in all likelihood to help in ameliorating the later life of man.

Even superficial reflection suggests that striking changes occur in the function of important organs. Consider for instance the stomach. At first it tolerates and digests foods that are especially adapted to it, simple perhaps; but later substances of greater complexity are managed safely; finally a return to the earlier situation apparently takes place. There is an evolution and an involution of structure and of function. That there are successive changes in the case of the long bones and of the skeletal muscles it requires a mere mention to appreciate.

I have said that this is an ancient subject. Growth, in the sense in which I am using the term, means successive changes in an organism both from the point of view of its bulk or mass which increases, as also from that of the progressive differentiation of all the tissues and organs of the body. Nor is the term confined to that stage in which bulk or mass continuously increases; growth continues also

during the period of involution, of decline, of old age. Growth now is negative where before it was positive. Parallel with change in bulk there is continuous differentiation in the intimate form and function of the organs and tissues, always in a forward direction, never backward to an earlier form—never as we say reversible. The idea should not be gained, however, that the rate of this change through life is uniform; on the contrary every effort to describe the whole of it in the form of a single curve equivalent to a single mathematical expression has met with failure. Brailsford Robertson,³ among the more recent to make the attempt, was obliged in describing the curve of metabolic rate and the attending weight curve to divide the life span into three parts, infantile, juvenile and adolescent, each of which required separate description and equivalent mathematical expression encumbered with variables so complex that to understand the process simply becomes too difficult. Nor does the organism as a whole grow uniformly, sometimes it is this organ, the thymus gland for example, which exhibits accelerated growth—sometimes another.

Theories of Senescence. Murray and I⁴ have recently been engaged in analyzing the various aspects from which speculation and research have been concerned with this subject. There have been essentially mechanistic and teleological theories. As a type of *mechanistic theory* may be taken Herbert Spencer's, that matter during growth (and evolution in general) passed from simple and homogeneous to complex and heterogeneous states. This change implied an integration of matter and the dissipation of motion. To show how this generalization became applicable in organisms, either unicellular or multicellular, the life of a single cell may be cited. In the protoplasm, solid particles were imagined to accumulate and to stiffen the substance; the walls became less permeable to the entrance of necessary, perhaps foreign matter; the electrical conductivity of the cell diminished. In the nucleus similar changes took place, except that here these transformations were even more conspicuous. As time went on, the pigment, the so-called metaplastic granules multiplied, and the excretion of substances elaborated in the cell became more difficult. When on this account the relation between intake and output of the cell became sufficiently unfavorable—the cell—the organism—died. Many suggestions have been made as to how, precisely, changes like this take place. So far no suggestions regarded generally as satisfactory have been adopted. The behavior of silicic acid, for instance, supplied an analogy. It is well known that this substance though a suspension when fresh, gels on standing. Birth represents a fluid state, a state of suspension; death an immobile one. This is the simplest of such notions. Other mechanistic theories involve the idea of control of the processes of growth by some substance manufactured, for instance, by one of the ductless glands, or by some tissue which

somehow develops relatively a more active metabolism and by so doing leads on the other tissues less favorably endowed. This is Child's⁵ idea which has been tested by him in many interesting experiments and which he thinks represents the presence of metabolic gradients. There are other theories of this class, but these illustrations suffice to indicate the sort we have designated as mechanistic.

Instead of attempting to "explain" the phenomena of Nature, to use Hobson's phrase, *teleological forms* of statement have been employed. The behavior of an organism or of a system may be examined with the view to learning whether its mechanism tends to satisfy a purpose, of course not explicit. I might cite the second law of thermodynamics as an example of such a theory, which states that all energy tends toward a minimum. Aristotle suggested a crude statement of the law when he supposed that in a newly born creature an amount of innate heat was implanted sufficient to carry it through life; in its course this was continuously dissipated. Death was the state which documented its complete disposal. Henderson's "Fitness of the Environment" is another example of this way of thought. It is the function of science and its methods according to theories of this sort to explore the justice of the view which is advocated. The difference between the two methods of viewing natural phenomena suggests for a teleologic one the possibility of adopting a direction for research. The theory presents the "Fragstellung." I need not recall other examples.

These being the theories, investigation has in practice been conducted with the view to ascertaining what *changes in form or matter*, that is to say in anatomy, and what changes in function, that is to say in physiology, may be detected. The construction of weight curves I have already mentioned. To describe successive structural changes at the beginning of life is the function of embryology. But after this early period when the rate of change becomes slower, there has been less interest in describing body and organ and tissue growth. To microscopic changes, more attention has, however, been paid. I recall measurements of the nucleoplasmic ratio which Minot⁶ thought decreased with time but with which Hertwig⁷ later disagreed. The difficulty of ascertaining this relation has led others as Le Breton and Schaeffer⁸ to attempt to estimate it chemically as purin and nonpurin substances.

Chemical differentiation may be regarded as an ultimate form of anatomic structure. Research in the direction of defining constitution in this way has also been attempted. Desiccation, or decrease in the concentration of water, is, for example, one of the commonest observations in the aged, having as a consequence increase in the concentration of nitrogen. In certain animals, the concentration of hydrogen ions in the plasma (as in guinea pigs) and in the blood (as in chicken embryos) has been studied and is now known to alter, as is likewise in man the tolerance to sugar and its concentration in

the blood. There can be no doubt, therefore, that the body undergoes both structural and chemical changes.

Through life there are *changes in function* also. To measure certain of them has been attempted in a variety of ways. Conklin,⁹ and indeed most writers on the subject, has shown that with time there is slow decline in the metabolic rate; Osterhout,¹⁰ that the permeability of membranes decreases; Child's⁵ experiments indicate a decrease in susceptibility to anesthetics in simple organisms; Murphy¹¹ and others, that susceptibility to infection differs in succeeding periods, irrespective of the history of exposure. Clearly the body is subject to change; clearly also its changes can be described. If we are to know the body these changes must be systematically investigated. To possess this knowledge has important consequences both for hygiene and therapeutics.

Factors which Modify the Process of Growth. Concerning the influence of heredity and of infection in early years on the process of aging or on the duration of life something should be said. Certain *infectious diseases*, as measles, pneumonia, malaria and varicella, are not now regarded as having an influence on the natural normal growth of heart muscle. But others such as tonsillitis, rheumatic fever, diphtheria, typhoid and scarlet fevers are not without effect on the heart. It would be going too far perhaps to say of the latter group that the nature of the injury to which the heart is subjected is known precisely. Insofar as this is confined to the valves, the outcome need not be supposed to be different from that which is expected when these are affected by other diseases, though two types must be recognized—one a destructive process, the other a productive one. But when the muscle of the heart is also involved, the issue may be different. It is unnecessary to describe the initial lesions—the focal necroses in typhoid fever; the destruction and regeneration of muscle fibers in diphtheria; the lesion still unknown in pertussis but attended it seems, at least occasionally, by enlargement of the heart, about the end result of which there is still no exact information; the essential Aschoff body in rheumatic fever. How much the effect is one of destruction of muscle fibers, how much of genuine regeneration, whether fiber is replaced by fiber, or whether in the end there are fewer than before or whether more; whether the fibers or some of them are replaced by connective tissue which itself has an influence on the subsequent process; whether the sole ultimate effect is hypertrophy; whether inflammatory tissue survives as scars or later contracts so that it is no longer distinguishable from perivascular connective tissue—all these are matters about which it is desirable to have more precise knowledge as well as better defined ideas concerning the end result of the processes on the duration of the life history of the fibers which survive. It seems necessary to recollect that beside the structural manifestations which are easily perceived there may be others more subtle which in

the nature of toxins or other poisons have had their origin in the original diseases and which having once influenced the behavior; perhaps minute and chemical of the muscle, thereafter continue to affect subsequent development in a manner the ultimate result of which is still unknown. This is the sort of effect about which no more than speculation may be indulged. Of one thing only is it possible to be certain; if actuarial experience persists in finding that normal expectancy is altered when one of these diseases has been a factor, the search for the condition underlying this result must be intensified. More for the moment cannot be said.

The influence of *heredity* is a different matter; the evidence here so far is in no sense anatomic—at least so far as the heart muscle is concerned, but rather statistical. There is, of course, the popular natural history which refers to the arteries. But about this there seems now to be doubt; Pearl thinks that even beyond the state of these, the degree of longevity of one's ancestors plays a determining part, though on this point there is also dissent. The matter of the arteries—about the heart muscle itself there are no criteria—brings up for discussion the difference between age expressed in numbers of years lived or chronologic age and age manifested by physical states or physiologic age. The meaning of the difference is simply that a man may be older, or younger, so far as his physiologic state, which implies the number of years he is likely still to live is concerned than the number of his years, his chronologic age, would have led one to suppose. Interesting as is this distinction, and important when it is better understood, now it is practically impossible to appreciate in terms of structure and of course of correlated function how either acceleration or retardation in the life process may have taken place. Nor is it as yet possible to be certain whether any environmental influence may have had a share in the process—such as the more exacting nature of modern life in the way either of greater speed of motion, greater competition in the economics of living, greater complexity in the arrangements of existence. Many a captain of industry, many a legal luminary, many a professor of classics, still lives out his allotted days.

Indulgence in athletics, such as rowing, football, baseball and track, seems to exert an influence on longevity as Dublin has recently shown in an unfavorable sense—but whether this influence is constant and to what mechanism it is due, it is not yet possible to be certain. The effect of overexertion on the heart and on the hypertrophy of its fibers and the probability that muscle once in this altered state survives a shorter period of time than when the processes of life are permitted to proceed at a customary natural tempo must be studied in this connection. Primarily the method of the investigation must be statistical; later the facts may become expressible in physiologic or chemical terms.

Classification. The study of man will I believe go forward best when it is related to the main stream of biologic thought. Against this background, it becomes easier to understand what variety of phenomena must be investigated in order to understand better the diseases, so-called, of old age. It is necessary first to enquire what are the phenomena of old age. Is every complaint, is every deviation from a preconceived normal, of the senescent organism to be regarded as disease? Are certain disorders to be anticipated, natural and inevitable, or, are there not also those which need not be anticipated, which are unnatural and are perhaps preventable? Do these two groups form distinguishable classes?

It is not my intention to make a comprehensive definition of disease, but rather to indicate that if the term disease is retained to designate all the ills to which the flesh is heir, there may be profit in attempting to distribute the phenomena under headings which describe more nearly how they came into being—whether, for example, as accidents such as infections or as accidents dependent on growth.

Consideration of the nature of growth suggests the probability that as part of it, may be reckoned occurrences which are now classified as diseases. If they are not diseases, a restatement is required of the definition of disease. The term disease then becomes applicable to phenomena which, from the point of view of growth, that is to say of the aging process, are not or need not be anticipated, are unnatural, or are preventable. If this distinction is just, it becomes necessary obviously to class certain occurrences as disease and others as phenomena of growth or of progressive differentiation. The extent to which this classification is possible or practicable depends on the amount of knowledge of the nature of the aging process which is from time to time available. This knowledge is still so slight that transference from one to the other class, from growth to disease, of many phenomena must necessarily take place until their nature is satisfactorily defined. But the establishment of classes is important here, as always in science. This is a matter not merely of words. The designations may be chosen differently. The term disease may be taken to include both classes—that which involves the processes of growth and that which accounts for the accidents of existence. There is, moreover, a practical need for this method of thought and procedure. Prognosis and therapeutics depend upon it. A process which is preventable or curable invites a different order of attention to its study and relief, from one which, like the progress of life itself, renders effort with such an object both aimless and futile.

The Growth in the Heart and Circulation. I have thought it proper to preface these remarks to what I intend to say on the subject of the heart muscle in old age, first because I am unaware that this aspect of the matter is often the subject of current thought and description

and second, because it serves to illuminate this subject which lies peculiarly in its province. With improvement in hygiene, more and more people come into the position of realizing their natural and allotted span of years. For this reason, the structures which appear to bear the brunt of the stress of life are the heart and the bloodvessels. I say "appear to bear this brunt" because medicine and physiology, being still youthful sciences, find it useful and easier to think in mechanical terms. It is not that other organs and tissues are not also exposed to wear and tear, but that the mechanical stress of the heart and circulation is obvious.

In the circulation, the question as to how aging progresses from the point of view of *function* has been investigated in a number of directions. It is known, for example, through the careful study of Faber and James,¹² of Alvarez¹³ and of Burlage¹⁴ that curves descriptive of systematic changes in the blood pressure may be drawn. Before the publication of these investigations, data less refined than theirs were already available. There is still an impression, however, that further study, still more careful selection and precise management of the material is required. Then, Gilbert¹⁵ has discovered a change in the degree of inhibition which the vagus nerves on being pressed exercise in the degree of their control of the rate of the heart; Crawford¹⁶ studied a related phenomenon by injecting atropin and observed the effect on the heart of releasing it from vagus control. Both found that their result could be stated in terms of age.

That the bloodvessels undergo change is another of the observations of daily life. Do we not say "A man is as old as his arteries?" Friberger¹⁷ and later Bramwell¹⁸ have studied this matter in an interesting and ingenious manner. It is well known that a fluid of a certain consistency flows at a rate through a vessel, depending on the elasticity of its walls. Bramwell found that at the age of five years, blood flows at the rate of 5.2 meters per second; as the vessels stiffen with years, the rate rises conspicuously so that at eighty it has mounted to 8.55 meters. The increase is striking—from 5.2 to 8.55 meters per second. A corollary that might have been expected because of stiffening of the vessels, is the observation by Daly¹⁹ that the arterial system of young animals can accommodate more blood relatively speaking than that of older ones, a function which he called the "potential capacity increment." These and similar researches may readily be believed to form the bases of new and important concepts of the behavior of the circulation.

In the heart, phenomena of growth and change are also encountered in its *form* and *structure*. The heart grows. It changes its form during the embryonic period. A simple tube becomes a complex system of cavities. The orifices which accommodated the fetal circulation change conspicuously; the organ becomes adapted

to the circumstance of aërial respiration. The wall of the right ventricle which was at first thick later becomes thin relative to that of the left ventricle. These matters of form having become adjusted at birth, increase in size continues to take place. Just what the course of this is, is known tentatively.

Whether or not the size of a heart is normal, is one of the most important matters for the clinic to be able to ascertain. The simplest data are those obtained by weighing postmortem. Tables expressing this information are available, but they are scarcely satisfactory. What is natural for a given race, constitution, age, height and weight needs careful separation from measurements obtained in cases where these factors are either unknown or disregarded; or where the effect of disease, no matter what its nature, has been permitted to influence the computation. Were these data all given their due importance, it would be possible ultimately to be in possession of tables accurately descriptive of each of the relations which we require to know. The heart of a Japanese of a given age and height may obviously yield a different figure from that of a north German. Were the facts known it would be possible to state that the weight curve of hearts bears a definite relation to that of their proper bodies and that these curves describe certain characteristic changes with time. In a given case, a deviation from the natural state could then easily be ascertained.

To weigh the heart postmortem is then the simplest way of learning its absolute and relative dimensions. But in the clinic we are driven to substitute methods of measurement. Percussion now practised about one hundred years, since its introduction by Auenbrugger and later by Corvisart and modified in many directions since, is the earliest of the methods. Before 1800 the clinic was without methods. Since 1893, the use of the Roentgen ray has become a valuable adjunct to the earlier techniques. Use of the general structure of the individual is made by relating the diameter of the heart to that of the chest. But to estimate the relative dimensions of the various chambers of the heart, these methods are inadequate. To be adequate requires possessing all the data mentioned in the case of weighing but in addition, knowledge of the shape of the heart and its position in the chest, two factors often mutually dependent. I refer to the so-called vertical, pendulous, or hanging heart, in contrast to that which maintains a transverse position. Whether a given heart is enlarged depends furthermore on its initial position and size. A vertical heart, the subject of mitral stenosis may increase greatly and may yet fail to extend as far as the left midclavicular line. It may in fact appear smaller than a heart of normal size which lies in a horizontal position.

It is necessary in practice to ask, What should be the size of *this* heart—is this one enlarged? This question is the beginning of the

analysis of the state of the heart. To answer it, it is necessary to draw on knowledge of the natural history of man—which is unfortunately still meager.

Manifestations of growth are conspicuous also in the *muscular apparatus* of the heart when this is examined histologically. At the very beginning of its beating, there is doubt whether any structure characteristic of the later fully developed contractile element is present. There is fair agreement that at first individual cells exist. Later these, by some method, how is not yet clear, become modified and coalesce so that the well-known syncytium comes into existence. How the bulk of the heart increases, despite the numerous researches which have been devoted to this end and the many theories which have been proposed is not yet known, either in the longitudinal or in the transverse direction. After birth histologic changes do not cease to take place. Longitudinal striations and transverse discs occur early, but intercalated discs make their first appearance at birth and increase in number and complexity throughout life. But about the nature and meaning of these there is no knowledge. Pigment begins to form about the tenth year and is deposited in a bipolar fashion about the nuclei. The amount of this increases progressively until in the sixth or seventh decade it lends to the appearance of the muscle a brown color. It is known as brown atrophy to pathologic anatomists, but there seems little doubt that its occurrence is a natural, normal phenomenon. The nuclei themselves undergo change, becoming larger, more irregular and on cross section seem to present grooves along their long axes. All is in a state of continuous change. An additional word should be said about transverse discs. During the period when the muscle is taking on a brown appearance, these also change. Their height becomes progressively smaller, so that in later life they seem compressed. This appearance together with the increasing number and complexity of the intercalated discs is so characteristic as to render it possible to distinguish microscopically old from young muscle.

As to the meaning of all these changes for function, little can be said aside from recalling that general knowledge, which is awareness of the fact that with advance in years comes decrease in bodily vigor and strength. But what is responsible for the change is less difficult, within very circumscribed limits, to define. Water, certainly, is one of the important constituents of the body; there is little doubt that its concentration suffers a conspicuous reduction in the case of most elderly individuals. It is probable that heart muscle takes part in this general process of desiccation and that it is this which is responsible for the change.

Just as the muscle is complex in structure, so must it be supposed that its *chemical structure*, its "Bausteine," is complex. Beside water, there is glycogen, and fat, especially of the double refracting variety and the protein substrate. Undoubtedly all these undergo

important alterations though no beginning has been made in describing them. The total result is, however, apparent; the muscle of the aged is a different muscle from any that preceded it.

It is necessary now to discuss the importance of hearts obviously larger and obviously smaller than a general established average, those which have become *hypertrophic* or *atrophic*. Karsner, Saphir and Todd²⁰ tell us what changes the muscle fibers have undergone in hypertrophic hearts. Here there is no change in the number of units but an increase in the diameter of the individual fibers. In atrophic hearts, on the other hand, there occurs a genuine reduction in the number of units. Of especial interest are the results in atrophic hearts. That these exhibit actual diminution in the number of fibers has consequences which are important in developing ideas concerning the history of the muscle. An understanding of the circumstances is important in which heart muscle, when put to strain, can hypertrophy and also when, under other circumstances, it can regenerate. And it is also important to learn whether and how far these functions are changes dependent on age.

Concerning the history of change in the *bloodvessels* of the heart, it is necessary to possess intimate knowledge: so much of the life of the muscle depends on them. Gross²¹ by means of injection preparations has made signal contributions to this subject. At birth the number of vessels, relative to the left, is somewhat in excess in the walls of the right ventricle. Later, the situation is reversed. After the fifth or sixth decades, there is another change; the relative differences become more significant but the absolute ones, striking; in the walls of both ventricles there are relatively fewer vessels, sometimes so few as to awaken wonder that there can still exist a sufficient blood supply. The mechanism which underlies this appearance it is important to examine. Does it depend on involution of the *vasa vasorum*, as Winternitz²² thinks in certain definite connections, and so on down to the very capillaries, or is it a process primary in the intima or media? It is a mechanism about which there is as yet inadequate knowledge but one without doubt which is important in understanding the general process which transforms the heart as a whole.

I come now to consider the meaning of all that I have been saying in the attempt to comprehend the diseases so-called of the heart in old age. Aschoff and Tawara,²³ in 1906, declared that for weakness of the heart muscle, for heart failure, they could find no histologic equivalent. One wonders whether this generalization would be adopted if it were made to include the considerations I have been urging. Aschoff and Tawara were thinking of sudden death, especially in connection with infectious diseases—I, of the gradual differentiation of the body. It is of course necessary to weigh the possibility of the occurrence of acute heart failure at all ages since naturally it may take place also in old age. But that is another

matter from the object of present interest from studying the association of progressing weakness, of progressing failure, with progressive decay.

Clinical Manifestations of the Senile Heart. Beside changes in the proper muscle fibers, in the bloodvessels, and in the constituent tissues, two additional sorts may be recognized; first collections of cells which are foreign to the heart and which are usually associated with the concept "*inflammation*," and second, the bundles and *masses of connective tissue* which are found either separating muscle fibers or so disposed that muscle fibers are found among them. That such tissue occurs after infectious diseases is, of course, well understood. These events are usual in youth. But in older people, apart from an association with the process of infection it is still unexplained and is not to be regarded as characteristic of old age. Lesions, changes, occur but not what is ordinarily recognized as inflammation. There is no myocarditis, as this phrase is generally understood. I shall return to this subject.

Of anatomic changes, I have traced two varieties, first that connected with what is already known of aging in heart muscle, its desiccation, its pigmentation, its changed nucleus; second that connected with what is already known of new elements as evidence of inflammatory processes and of connective-tissue growth. It is just as, perhaps even more, important to study the heart of advanced age from the viewpoint of *function*. Two orders of disability require examination—weakness and pain. *Weakness* must, it seems, be distinguished from fatigue. By fatigue, I mean a phenomenon which is asymmetric to, out of tune with, the performance of other still vigorous structures and organs. Except for this manifestation on the part of the heart, they continue to be capable of exhibiting the behavior of robust health. By weakness, I mean that phenomenon of symmetrical disability which, as the result of age, involves the whole organism in uniform progressing decrepitude. Similar phenomena may perhaps characterize cachectic states as in malignant neoplasms or pernicious anemia. But these I think fall outside my definition in that in some way their development may be found to be asymmetrical, inharmonious. Weakness, on its anatomic side, I have just been predicating, so far as contemporary knowledge permits, as the desiccation and pigmentation and perhaps other changes still unknown of the heart muscle. It may perhaps be regarded as the most natural of the manifestations of involution. The pump, without putting too fine a point upon it, is, after all, the life-distributing organ of the body. Its estate is still high, even if the estimates of a later physiology have displaced it from being, in Harvey's phrase, the sun of the microcosm. For the body to become weak, for the heart and indeed all the tissues to become desiccated and to undergo the many other chemical and physical changes which are easily conceived to be necessary if the

equilibrium of the forces and substances which are involved is to be maintained in harmony, is the natural result in the aging organism. How long the span of this process may be, whether if it be a lingering sweetness, it may be long drawn out, experience does not yet tell us. But of one thing surely there may be certainty; this process cannot be prevented by any means so far discovered. Hope, if hope it be, which is held out in this direction seems bound in some sense to be frustrated. Of far greater usefulness is the effort by whatever hygienic or other means to provide an environment in which the aging process may be accomplished to its best and most undisturbed advantage.

I come then to that most vexed problem of *pain*. There is little doubt, as Stewart²⁴ has pointed out, that the circumstances under which it occurs are now differently described from those which Heberden first indicated. Nor are there now many observers who believe that affection of the heart can give rise to one variety of pain only—either in distribution or in character. There is pain which is slight and brief and recurs during a long term of years; there is pain which, though brief, is intense and is accompanied at once by death. There is pain which is scarcely experienced at the precordium without radiating, but there is also pain which does not radiate. There is pain which does not raise the suspicion that it emanates from disorder of the heart; it is referred to the abdomen and is described as “severe stomach-ache” or “acute indigestion.” There is pain which occurs only in connection with exertion, as in Heberden’s description, designated as *angina pectoris*; but there is also pain which occurs in sleep and in the dead of night.

It is unnecessary to recall how difficult, how impossible it is to distinguish these varieties with the hope of assigning all of them to appropriate lesions. They differ in location, in duration, in radiation, in character and in the time and circumstances of their occurrence. Despite all the thought and investigation which has been devoted to this matter, only two structural abnormalities have been proposed for correlation with pain. Both are lesions of the coronary vessels. Herrick²⁵ deserves credit for having discovered what appears to be a sound anatomic basis for one variety. I refer to the association, not the lesion. The condition now is designated *thrombosis of the coronary artery*. It is not my purpose to describe this disease, if disease it be, in detail. There seems little doubt now, because of the nature of the pain, the presence of fever, leukocytosis, and pericardial friction rub and the coëxistence of thrombosis of a coronary artery, that this complex at least is a clinical entity. I wish rather to examine into the classification of this entity—into the age, and the nature of the lesion and then to indicate whether an understanding of prophylaxis and therapy are better served by regarding its occurrence as a manifestation of the aging process or straightway simply as a disease. Since its histogenesis is unclear,

an enquiry concerning it may repay study. On two points, there is knowledge. First, there occurs involution of the capillary vessels throughout the body and presumably also in the heart. Whether this process is a matter only of number or whether in addition a qualitative change develops in the endothelium is unknown—but a subject this of first importance. Second, there is an involution, as Gross²¹ has shown, in the number of vessels of the heart. A third point may be added; Winternitz and his pupils to whose investigations I have already referred have insisted that in many arterial lesions the essential alteration is to be found in the vasa vasorum and that it is the alteration in them which is essentially connected with the occurrence of thrombosis. I am not aware that specific study has been made of this process in the coronary artery. The final link in the chain of argument is there. If thrombosis of the coronary artery depended on capillary involution, and if it were this essential process which underlay the occurrence of thrombosis of these particular vessels, there would be a somewhat clearer understanding of the whole matter. Meanwhile, one can do no more than say “somewhat clearer” because there remain other factors which still require analysis. Is this the method which accounts for the reduction in the number of vessels throughout the heart in advanced years? The situation is obviously different from that in early growth in which the number of vessels respectively in the walls of the two ventricles undergoes a state of relative change. It is not known to be a fact but the difference between youth and age may depend in this respect on the maintenance of a fixed number of vessels in which mere enlargement, expansion, occurs as the bulk of the right ventricle increases, but on the development of new vessels on the left side. The problem of increase and decrease in numbers need in short not be the same in youth and in old age. But to return to the situation in old age. If this is the process in the cases which are now familiar, is it this same process of capillary involution as just suggested, which is responsible for the natural disappearance of other vessels, and, if so, does evidence exist histologically that these others have gone this same course: and again, if so, how does it happen that change in these others is not accompanied by clinical manifestations? These are questions which are more readily asked than answered. The suggestion may, however, be ventured that, as a statistical matter simply, the chances are that smaller vessels, being more numerous rather than larger ones, are involved; that in consequence smaller areas, or volumes, of muscle are affected; and that, therefore, being relatively speaking silent no injury results sufficiently great to occasion clinical manifestations. But it is not even necessary to suppose that even small occlusions occur without the occurrence of distress; many an individual in middle life experiences some sort of discomfort on occasion—it may be trifling and passing or even transient severe pain; it may be the sensation of

premature contractions; it may be that because he has complained electrocardiograms are taken and reveal small or sometimes striking changes in their essential form. Who knows but that these are the cases which, in the absence of all other reasons, exhibit postmortem the appearance of disseminated sclerosis or of old infarction. Wearn²⁶ believes he has found it; others are silent or doubt whether it occurs. The collection of leukocyte counts and of temperature curves taken at such times may in the light of subsequent events yield important evidence, if this is the natural course.

The process which I have described may be, I am suggesting, at the root of thrombosis of the coronary arteries. I mean to be careful merely to suggest its possibility because of the use I wish to make of the suggestion in the subsequent argument, and to do no more than to propose it for further exact investigation. A knowledge of the fate of the capillary vessels at the end of life, as at the beginning, is a matter of first importance. If the assumption may tentatively be made that thrombosis of a coronary artery depends on the involution of capillaries, of vasa vasorum, the inference is justified and clear that the affection is incident to the process of growth, of continuing differentiation. Its occurrence is no accident, as an infectious disease is an accident, but a major among many similar minor occurrences, attaining conspicuous proportions merely as a matter of chance by involving a large rather than the usual small vessel.

I am aware of the fact that this view has important consequences for a general definition of disease. May it not disturb the usually accepted notion of the nature of certain diseases, so-called, of the kidneys? How shall affections like diabetes insipidus or indeed certain, especially youthful cases, of diabetes mellitus be classified? How affections attributable to other malfunctions of the glands of internal secretion? How that melting pot now designated arteriosclerosis? I do not raise the issue with the view to proposing solutions now for all these questions. They must be studied each on its own merits. It may very well be that in connection with growth, with the differentiation of the body, its tissues and organs, two possibilities exist. (1) An affection may develop in the embryo because growth has taken abnormal courses due to coarse processes of maldevelopment as in *cor triloculare*, or *spina bifida* or perhaps idiocy. (2) The malignant tumors, exophthalmic goiter, and pernicious anemia may belong to a group where the defect is more subtle. In old age, on the other hand, there need have been no initial defect in growth—growth and differentiation may have taken place without error; all tissues may duly have come into being and have performed their usual functions. When, as in coronary thrombosis which I am proposing tentatively as an example, an accident of growth takes place, it is not an accident of development, but a chance incident in that further differentiation which we call senescence. Those who wish to call this accident a defect will wish to distinguish

between defects of evolution, the events of youth, and defects of involution, the events of old age. The great importance of both, from the point of view of therapeutics, is that at the moment there appears to be no prophylactic relief. For both, there may eventually be the possibility of rational interference, especially if or when the process which underlies the defect is understood; but that the therapeutic procedure be rational, irrespective of whether the defect has occurred by accident or design, is in each case the condition of effective interference.

I have dwelt at length on the subject of coronary thrombosis because of its class it is the best defined of the maladies of the heart and could for that reason serve as a more satisfactory illustration. The choice I have made may be unwise or incorrect but the thesis I am defending is, I believe, necessarily sound nevertheless. The body does grow; it does differentiate, it does age, and it dies. If it attains the total duration of its natural span, it dies by a mechanism as natural as the one by which in common parlance it grew.

Angina pectoris, though in many minds it no longer accords with the description which Heberden gave of it, is the second condition in which there is general belief that pain is associated with or is dependent upon abnormality or malfunction of some sort of the coronary arteries. The pain is different from that usually described in coronary thrombosis. There it is tearing—here squeezing and viselike; there precordial, here apparently more often referred to the abdomen; there it radiates, in its most characteristic form, to the left arm, here it fails to do so. What the state of the coronary arteries is, whether atheroma or sclerosis is present or simply spasm of a vessel, not yet sclerosed or sclerosed only in part, is a subject recently discussed with much penetration by Keefer and Resnik.²⁷ In their view, anoxemia of the muscle due to affection or disease of the coronary arteries or of the aorta brings on characteristic pain. Others certainly may still find objection to this conclusion. Whether Sutton and King's²⁸ and Percy's²⁹ experiments in dogs in which they managed at will, by constricting a coronary artery, each time to elicit manifestations of pain are valid representatives of the clinical condition, it is still too soon to say. Keefer and Resnik's analysis and these experiments are useful contributions toward a knowledge of the subject. Whether this affection is to be reckoned as a disease or as a manifestation of growth depends obviously on ascertaining its mechanism more precisely. The whole subject is still too vague. Obviously this too occurs, as coronary thrombosis does, in the old rather than in the young. The mechanism which Mackenzie proposed, exhaustion of the heart muscle or of acute dilatation in the sense that this occurs in other hollow muscular viscera, the vermiform appendix or the gall bladder, finds no favor with Keefer and Resnik any more than does that of Allbutt who regarded this phenomenon as initiated at the root of the aorta.

But the condition itself is too ill defined, its pathogenesis and mechanism still too inexactly understood to render an attempt at classification profitable.

Although usually not described in textbooks, there is a form of *pain* which occurs in the *middle aged*, of great interest and, so far as is known now, not associated with a demonstrable cardiac lesion. It occurs, as did that in Heberden's description of angina pectoris, in association with exertion and with exertion only. Prolonged rest of two, three, four or even more months relieves such cases; and certain ones, though which they are it is difficult to predict, it relieves permanently. Whether this variety is associated with an anatomic lesion in the usual sense is not yet known.

On the assumption that heart muscle as well as all the other tissues in the body, no doubt are in a state of constant differentiation, questions arise concerning the possibility of *repair* after an injury is inflicted or of compensation after a mechanical defect has developed. Unfortunately, knowledge in both respects is meager. Warthin,³⁰ Heller³¹ and others have shown in the case of diphtheria that in place of muscle which has been destroyed, new muscle fibers may develop. How frequent this is, and whether it is the rule is a matter about which one would like to know more. It was not an unexpected discovery, for in the growth of heart muscle there are investigations which indicate that differentiation may take place at a suitable time from persisting still undifferentiated cells. But the problem cannot yet be regarded as finally solved. In any case, it concerns young, not aged individuals.

That compensation for defects takes place is amply demonstrated in the case of valvular heart disease. Its mechanism is hypertrophy, enlargement of the individual elements of the muscle fibers, so far as is now known. It has been shown by MacKay, Addis and MacKay,³² by Arataki³³ and others that under certain experimental conditions the kidneys also exhibit this function of hypertrophy. But it has likewise been shown, that this is a function of time and that after a while it declines. Whether a time occurs when it fails entirely is unknown, though by inference this is unlikely. The rate may be much delayed, but skin healing does take place in the aged and fractured femurs do unite. The important point is that the difference between adolescent and senile reactions is striking. Those pathologic anatomists whom I have consulted have the impression that, although precise knowledge still is sadly wanting, compensation in the form of hypertrophy is a form of repair in old age which, if not wholly lacking, is nevertheless significantly incomplete.

Therapeutics. Concerning therapeutics, I wish to speak of two matters only, the use of digitalis and the meaning of operation performed on the cardiac nerves. There are those who think that giving *digitalis* to older individuals is accompanied by less strikingly beneficial results than when given to the young. The justification

for this statement is still largely unfounded. There are undoubtedly among patients individual differences; they are plentifully familiar in the young. But in addition it is necessary to make a number of distinctions of importance. In the first place, cases of pure affection of the heart must be separated from those in which the kidneys are also involved and in which there is edema. In the second place, the type of cardiac affection which is present should be described. In the third place, it matters what the rhythm is to which the heart is subject—whether the auricles fibrillate or flutter. These and other considerations require analysis. At the present time, though, as has been stated, insufficiently founded, the belief prevails that digitalis is a less effective remedy in the senile state. What the principles of a sound digitalis therapy are must await further investigation. Meanwhile, there can be no reason for withholding the drug from patients in which on general grounds it appears to be indicated.

What the meaning of *operating on the cardiac nerves* is, is intimately related, obviously, with the whole subject which I have been discussing. This problem must naturally be decided quite apart from any question of operative technique or of the selection for treatment of the particular structures which will ultimately be found to be part of the nervous pathway involved in the occurrence of pain. The whole matter is one of great interest not only in therapeutics but from the point of view of anatomy and of physiology. Many patients have in fact been materially relieved of pain by one or another of the operative procedures.

Section or excision of a nerve may have or may interfere with one of several possible functions. It may cut the reflex arc which is instrumental in causing pain. If it does that and nothing more, no harm, but benefit only may be expected to result. But whether it interferes with, alters or stops the process which gives rise to the pain is not yet known. There are those who have hesitated to advise the use of the method lest patients be led to believe in a false security, when, in point of fact, the absence of a warning pain may induce them to undertake exertions and to become exposed to dangers which it would be better to avoid. Other things being equal, the question may be raised as to whether the exchange of comfort for danger may not depend on a decision in which the wishes of patients may perhaps be consulted.

But more may be involved in an operation than simply influencing pain. The time is not long past when Gaskell was maintaining theses concerning anabolic and catabolic functions of nerves—in this connection the anabolic function of the vagus nerves. The form in which he held his view seemed subsequently to require modification in the light of experiments and deductions therefrom performed by Einthoven. But phenomena, such as Charcot joints, to mention only one of them, point to the trophic functions of nerves. It is impossible to say now whether cardiac nerves have such functions

nor if they have, by which ones they are exercised. If as is possible certain of the affections of the heart depend upon the processes of growth, the influence of appropriate nerves may not be negligible. Interference may either accelerate or retard the process. To stop the pain may actually injure the patient. Experience, not taking thought, will solve the problem.

It was not my intention to present the subject of aging of the myocardium in a systematic way. What systems there are, may be found in the textbooks. But if I have understood the purpose of this program correctly, one which reflects an interest relatively speaking new, and matured in a period of time surprisingly brief, since first I devoted my attention and interest to it, it must be to lay before you points of view or at least a point of view which has not been, because an interest in the natural history of man (apart from that slight spread interest in constitution as a factor in etiology) has not been current in discussions on the content or range of medical science. It has been my object to emphasize the fact that human beings are growing creatures. Their anatomy and physiology cannot be described completely if the description is made to apply to a selected period of life. Growth is a continuous process, always in the throes of change, constantly exhibiting new and altering phenomena until the phrase, "the child is father of the man," takes on new meaning. Child and man are indeed two distinct individuals. If their natures are different, so are the ills to which they are liable, and so the remedies which it is the high function of medicine to bring to their relief.

Summary. A more formal summary of what I have attempted to bring to your notice, should, I think, not omit reference to the theories which have been evolved to make clear to men's minds how old age may be brought about; I refer to what were called mechanistic and teleologic theories. They form the background which make understandable the detailed researches which were later briefly described. Researches which aid in illustrating this manner of trying to understand changes in the growth processes were cited, both from the point of view of anatomy and of physiology in general, but especially certain ones which show that in connection with the circulation, studies already undertaken, not always consciously, make it certain that profit will flow from more deliberate investigations designed from this point of view. Certain diseases, if so regarded, appear to depend for their explanation, as I pointed out, on the processes of growth, rather than on accidents dependent on the external environment. If a division of diseases due to accidents, on the one hand, and on the other to defects in growth issues from reflection of this sort, the significance of certain cardiac maladies, of which pain is a prominent complaint and which occur in advanced years, takes on a new or a different meaning, not only in comprehending their pathogenesis but also in making provision for their relief.

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INTERVENTRICULAR SEPTAL DEFECT WITH DEXTROPOSITION OF AORTA AND DILATATION OF THE PULMONARY ARTERY ("EISENMENGER COMPLEX") TERMINATING BY CEREBRAL ABSCESS.

REPORT OF A CASE OBSERVED DURING LIFE, PRESENTING IMPAIRED CONDUCTION, AND PARALYSIS OF RECURRENT LARYNGEAL NERVE FROM PRESSURE OF HYPERTROPHIED PULMONARY CONUS.*

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CASES of interventricular septal defect with associated pulmonary stenosis and dextroposition of the aorta (tetralogy of Fallot), are not infrequent in the literature; but the combination of a localized defect in this situation with dextroposition of the aorta but *without* associated pulmonary stenosis is extremely rare. The first case on record is a full clinical and pathologic study published by Eisenmenger,¹ in 1897, of a cyanotic man, aged thirty-two years, in whom the combination was correctly diagnosed during life by von Schrötter from the character of the physical signs, in that the loud precordial systolic murmur present was not transmitted into the vessels of the neck as is usually the case in the "tetralogy" but downward toward the apex and along the course of the pulmonary artery, and there was no thrill. So far as we know only two other cases have

* Presented at the meeting of the International Association of Medical Museums, Albany, N. Y., April 1, 1926.

been reported, both by Abbott, one the heart of a child, a specimen in the McGill Museum, and the other a man, from the service of Dr. Libman, aged thirty-five years, who died of a subacute bacterial endocarditis.² Moreover, a case, of congenital cyanosis such as the following in which the patient has attained adult life and has been studied clinically with Roentgen rays and electrocardiogram, followed later by necropsy, is still more worth recording. The patient was seen in this clinic on four different occasions over a period of fifteen months and though the particular nature of the lesion was not specified, a diagnosis of congenital disease of the heart was made. Of special interest also, from the clinical standpoint were the following observations: (1) evidences in the cardiogram of an abnormal disturbance of the propagated impulse (left bundle-branch block); (2) hoarseness for many years, and more recently aphonia, due to pressure on the recurrent laryngeal nerve of the enormously hypertrophied conus of the right ventricle, which showed in the Roentgen ray as (3) a greatly enlarged pulmonary arc (Fig. 1); (4) the termination by left hemiplegia with coma, shown by the subsequent autopsy to be due to a large cerebral abscess in the right frontoparietal lobe. The latter event is of great interest as pointing to a paradoxical embolism into the greater circulation of septic thrombotic masses from the venous circulation, an accident peculiarly liable to happen under the anatomic conditions present, in which a large dextroposed aorta rode above the defect receiving blood through it from both ventricles (Fig. 5). Following is the report of this most interesting case:

Case Report. V. B. (Case No. 17098) male, aged twenty years, entered the Clinic on account of a goiter and hoarseness and aphonia. He was seen early in March, 1924, giving a history of hoarseness and aphonia since about the age of thirteen years. The patient had never been strong but had lived on a farm and done many of the tasks there necessary. He had a small goiter which had been present some months and which was the main reason for entering. There was lack of endurance, dyspnea after increased exercise and cyanosis of dependent parts. In the family history there was one brother who had a goiter. The parents were rugged farmers who had always been well and did not understand the shirking in work that ill health may force on one.

The examinations were directed mainly to the heart and the possible effect of the goiter on the cardiovascular system. On fluoroscopic chest examination, a general hypertrophy with marked prominence of the right auricular curve and slight prominence of the left was noted. The pulmonary conus was unusually prominent, the heart action rapid, overactive. Pulsation was transmitted especially to the right hilum and pulmonary conus. No substernal thyroid was seen nor was the liver or spleen visualized. A slight increase of hilum shadows was noted.

In 6-foot heart films the measurements showed a moderate general hypertrophy. The curve of the right auricle was decidedly prominent, the right ventricle full and rounded, the left auricle prominent, but shaded over by a marked prominence of the pulmonary conus (Fig. 1). The roentgenologist's conclusion was that this was a congenital heart condition, most likely a pulmonary stenosis with patent ductus arteriosus (Botalli) and a general hypertrophy, especially of the right side.

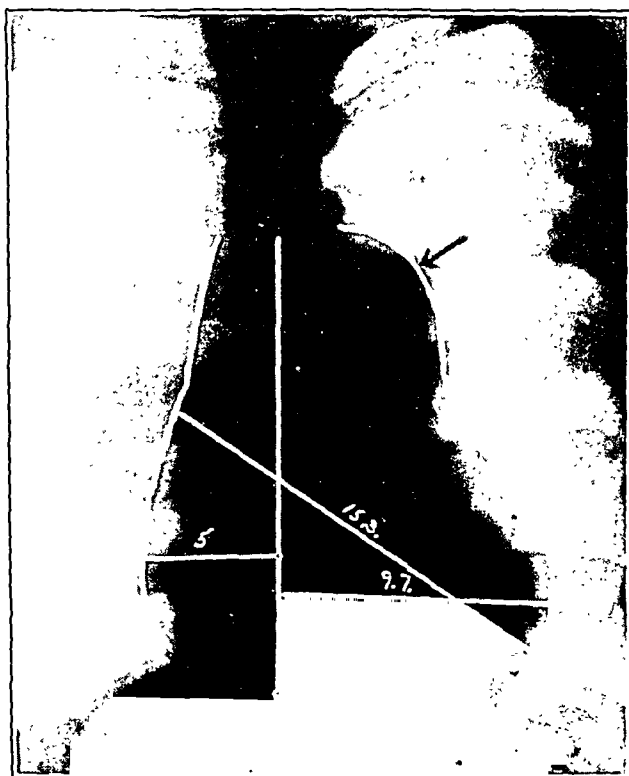


FIG. 1.—Teleoröntgenogram (6 feet) taken of the heart at the first entry.

Heart	Weight
Teleoröntgenogram	Average normal 125 or 130
M. R. 5	3.7
M. L. 9.7	7.2
T. D. 14.7	10.9
L. D. 15.3	12.6

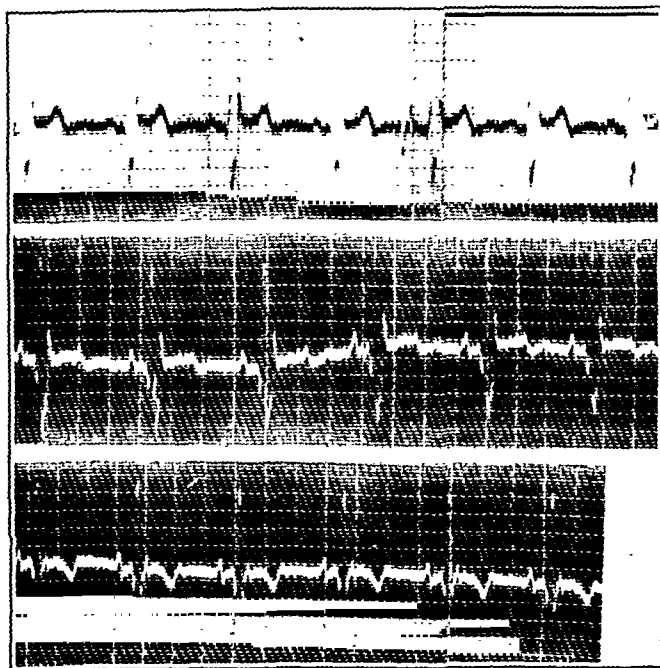


FIG. 2.—Electrocardiogram (Leads 1, 2, 3) taken at the first entry, showing right ventricular preponderance and split *R* and *S* waves. The *Q-S* interval is 0.09 seconds.

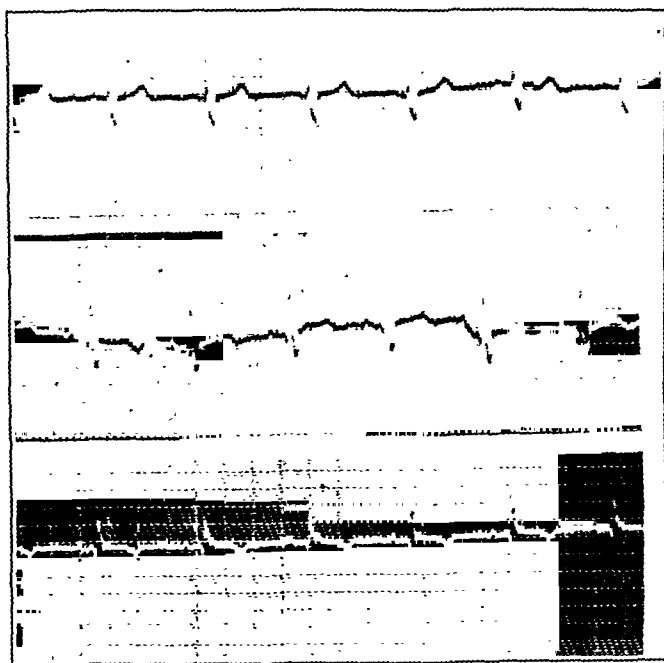


FIG. 3.—Electrocardiogram taken June 4, 1925 (third entry), showing right ventricular preponderance split *R* and *S* waves. The *Q-S* interval is 0.10 seconds.

Auscultation showed a loud systolic murmur over the heart, most marked in the pulmonic area, and a soft diastolic one to the left of the sternum. A cardiogram showed right-heart preponderance and a split *R* and *S* (Fig. 2). It was thought there was a congenital pulmonary stenosis and hypertrophy of the heart.

Eight months later the patient was again seen. At this time, a note was made that the patient was less easily made cyanotic and the diastolic heart murmur was not so loud as in the previous examination. The blood pressure was 110 systolic, 80 diastolic. There was some cyanosis of the peripheral parts, dyspnea on exertion and a loud systolic murmur over the pulmonic area. Cardiogram again showed a split *S*, a right heart preponderance, and slight delay of conduction thought to be evidence of incomplete left bundle-branch block.

Seven months after his second entry the patient returned. Again slight exertion caused dyspnea. His color was definitely better than at the previous visits, but was said always to be better in warm weather. A loud systolic murmur over the precordium and a diastolic to the left of the sternum louder than at the previous examination was noted. Blood pressure was 100 systolic, 70 diastolic. Cardiogram showed a split *R* and *S*, a right-heart preponderance and again evidence of left bundle-branch block (Fig. 3). The patient had returned on account of the thyroid condition. It was not thought this was causing any toxic symptoms so far as the heart was concerned.

On his final entry, July 28, 1925, the patient was practically comatose. About two weeks previously headaches began but he continued light work. He became nauseated, vomited and finally several days before entry became drowsy but could easily be roused. On entry, there was found a bilateral choked disk, paralysis of the left face and arm and an ill-sustained ankle clonus on the left. A loud, harsh systolic murmur best heard over the pulmonic area was again noted. He was given salt solution intravenously. The next day there was no nausea or vomiting, the pupils were dilated, the left leg was partially paralyzed and the left arm was noted as weaker than on the preceding day. Lumbar puncture showed increased pressure of the fluid, a cell count of 9, positive globulin but a negative Wassermann. The blood Wassermann was also negative. One specimen of urine showed sugar but another was negative for this, albumin was slightly positive, and many leukocytes were present. Speech became difficult, the heart rate was between 40 and 50 and the patient complained of much headache, but toward night became comatose. The next day the pulse became more rapid and he died early on the third day.

Autopsy revealed a rather slightly built and poorly nourished young adult male. The heart *in situ* was horizontal, the right auricle and ventricle markedly enlarged and the pulmonary artery enlarged, especially so in comparison with the aorta (Fig. 4). The pulmonary artery at the base of the valve measured 8.5 cm. and the aorta 6 cm. The left ventricular wall measured about 12 to 13 mm. in thickness. The pulmonary cusps were fenestrated and of unequal length, the posterior one being very voluminous and 3.5 cm. long, the left anterior 3 cm. while the right anterior was comparatively short, only 2 cm. in length. There was a small accessory coronary given off behind the left anterior pulmonary cusp. The mitral valve, as well as the aortic, was normal. The right ventricle wall measured 10 to 11 mm. in thickness. In the upper part of the interventricular septum just anterior to the pars membranacea septi there was a defect 2 cm. across (Fig. 5). The anterior and lower borders of this were muscular and rounded. The fibrous tissue of the right posterior aortic valve was continuous with the pars membranacea, and the medial tricuspid segment which formed the wall of the septal defect. The aorta arose partially from both ventricles

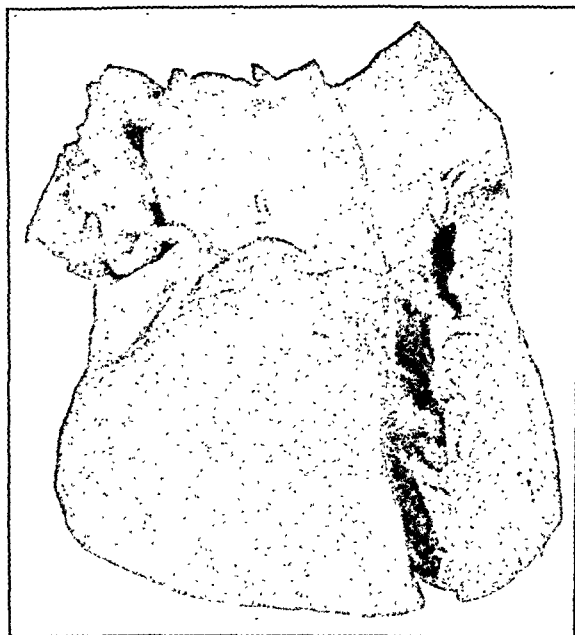


FIG. 4.—Photograph of heart showing right ventricle and pulmonary artery opened up. Note the thickness of the conus wall and the width of the base of the heart.



FIG. 5.—Photograph showing defect in ventricular wall through the opened left ventricle. A, right anterior (coronary) cusp. D, interventricular defect. Note thickness of ventricular wall.

and appeared rotated somewhat to the right (dextroposition). The conus of the right ventricle leading to the pulmonary artery was somewhat narrowed and had thick powerful muscles, the posterior muscle wall forming the anterior wall of the septal defect being especially thick. The tricuspid valve presented a deformity of the contiguous halves of its medial and infundibular segments which were attached without any proper differentiation of papillary muscles, the infundibular cusp into the posterior surface of the heavy muscular wall of the conus of the right ventricle which here forms the anterior boundary of the septal defect, while the left end of the septal tricuspid segment is in part fused with the contiguous margin of the infundibular segment but in greater part passes through the septal defect and after becoming continuous with the anterior segment of the mitral valve below and with the pars membranacea above, is attached here to the aortic ring just below the junction of the right posterior and anterior (right coronary) cusps. It thus serves to screen the large septal defect in the right half of its extent from the cavity of the right ventricle. A single, long, thick aberrant chorda tendinea passes from the free portion of the infundibular tricuspid segment to be attached by three branching filaments to the anterior border of the defect near the attachment of the main infundibular segment to this area. No signs of acute inflammation were found. A loose thrombus in the right auricle which was afterward observed is discussed later in this paper.

The thyroid showed a rather definitely enlarged left lobe, about three times the size of the right. On section, many small nodules were to be seen, some continuing dark-colored fluid. The right also contained small nodules. In the brain, the convolutions over the right frontoparietal area were flattened and an irregular yellow area was seen on the surface; this was soft to the touch and purulent material was obtained on puncture. Culture showed a *Streptococcus hemolyticus*. After hardening the brain, section showed a large abscess about 5 cm. across in the right frontoparietal region involving the motor area, internal capsule and surrounding structures. Microscopic studies showed a typical abscess of the brain and an adenoma of the thyroid.

Discussion. We have then here some typical findings of a congenital heart case with some confusing symptoms. The hoarseness was thought possibly due to the thyroid although this was not markedly enlarged. No disease of the larynx or trachea could be made out. Because of a possible goiter operation the heart was studied and a congenital lesion believed to have been found. From the enlarged right heart and high pulmonary arc and location of the murmurs, it was thought a pulmonary stenosis with persistent ductus arteriosus was the probable lesion. It was acknowledged at the bedside that the aphonia might possibly be accounted for by the enlarged heart, but at the time the thyroid was believed to be the cause. In his final entry, a diagnosis of increased intracranial pressure was made; but operative procedure was thought inadvisable on account of the heart condition.

Abbott, Lewis and Beattie³ have published two cases of interventricular septal defect with associated pulmonary stenosis and cerebral abscess following embolism, and collected 6 similar cases from the literature. These varied from six to twenty-five years of age. There were 6 males and 2 females in the series. They have

also collected 6 cases of open foramen ovale with brain abscess. Their explanation of a paradoxical embolism is apparently well-grounded. Their 2 cases had definite sources of emboli, in one an infected arm, in the other an acute appendix. Our case is less clear in this point as there was no endocarditis or septic lesion located, and the only source for an embolism that was demonstrable was a small pocket in the wall of the right auricle near the entrance of the superior cava containing loose thrombus, which was not noted at the autopsy but was located later in the Museum specimen.

Abelmann⁴ in discussing heart anomalies made the statement that these cases often die with brain symptoms. He did not, however apparently understand the significance of the brain symptoms as originating in a "crossed" embolism as did Ballet⁵ (1880), and as has been so clearly pointed out by Abbott and others.

In comparing our specimen with those described by Abbott and her associates³ in their article on this subject, we see that it corresponds to their 2 cases in the presence of a huge interventricular septal defect above which the aorta is displaced to the right, thus supplying a direct avenue for the transmission of an embolus from the right heart to the great vessels of the head and neck and brain. It differs however from their cases in the absence of pulmonary stenosis (as in their Case 2), or atresia (their Case 3), for the pulmonary conus in the case here described is roomy and thick-walled, and leads into a very large and greatly dilated pulmonary artery (8.5 cm. wide). Both conus and artery have here developed as in the normal heart, and have evidently undergone dilatation to accommodate the additional volume of blood received from the left ventricle through the defect in the left to right shunt that prevailed owing to the relatively higher pressure in the left ventricle, while the dextroposed aorta received a mixed current of venous and arterial blood from both ventricles above which it rides and transmits this to the systemic circulation, producing a raised oxygen-unsaturation in the capillaries there with resultant cyanosis (see Fig. 6 from Abbott and Dawson⁶). Clinically our case resembled pulmonary stenosis with associated septal defect in that there was a harsh precordial systolic murmur which on three occasions was observed to have its maximum intensity at the pulmonary area, and there was no thrill. On one admission, however (June 1925), it was described as diffusely heard over the entire precordium (that is, without point of maximum intensity) and there was always present along with it a distinct diastolic murmur on the left side of the sternum which was apparently the result of the pulmonary insufficiency, while the Roentgen ray plates, which show only a moderate (though definite) right-sided enlargement, with marked enlargement of the pulmonary arc, and the fluoroscopic demonstration of marked conus pulsation in this same arc with widening and increased pulsation at the hilum of both lungs (Assmann's sign) pointed definitely to a pulmonary dilatation (and

not to a stenosis as has been wrongly argued by some writers). Again, the late onset of the cyanosis at about the age of thirteen years, and the moderate degree of this that existed, together with the absence of clubbing argue also against the existence of an associated pulmonary stenosis, in which condition the combination of back pressure in the venous circulation resulting from the pulmonary obstruction combines with the high venous content of the arterial blood under the right to left shunt that prevails, to produce marked cyanosis and clubbing in all cases of long standing.

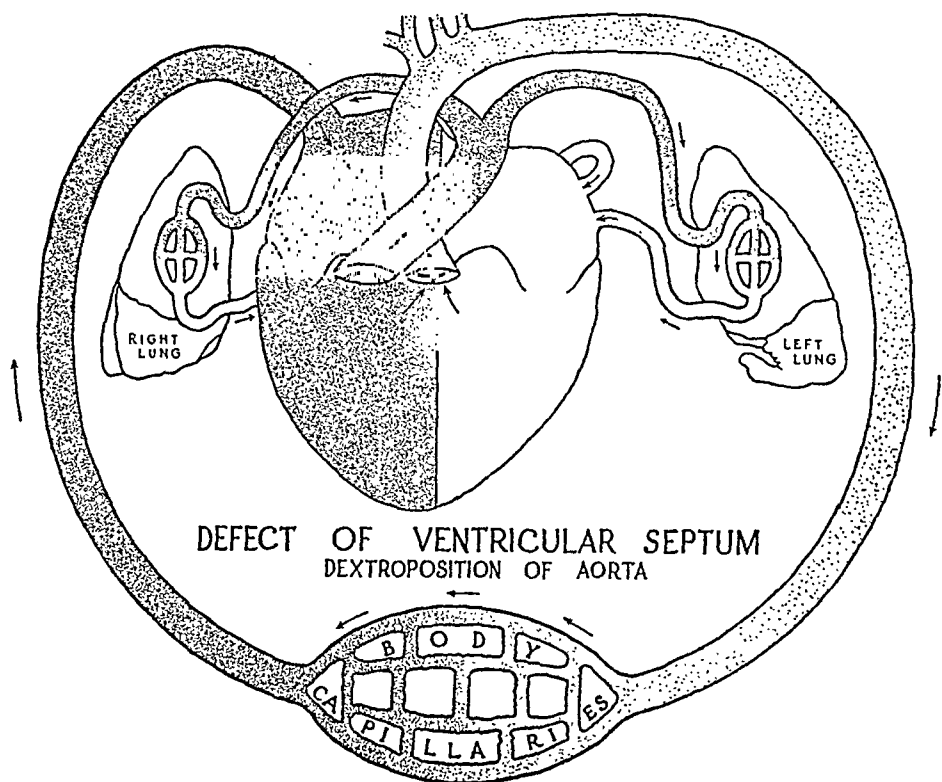


FIG. 6.—Diagram showing course of the circulation in interventricular septal defect with dextroposition of the aorta and dilatation of pulmonary artery (Eisenmenger type). The aorta is seen to ride over the defect, receiving arterial and venous blood from both ventricles leading to a moderate degree of cyanosis. (From *Clinical Classification of Congenital Cardiac Disease*, by Abbott, Maude E., and Dawson, Wilfred T., *International Clinics*, 1924, 4, 170, Fig. 9.)

In this case, therefore (in which it must be clearly emphasized there was no pulmonic stenosis), the presence of the enlarged pulmonary tract was clearly evidenced by the above syndrome, while the dextroposed aorta and ventricular septal defect were indicated by the moderate degree of cyanosis, and the curious shape of the heart in the Roentgen ray picture, which shows a widening to the right of the median line above, and a relatively small degree of enlargement of the right heart, the hypertrophy of the latter being apparently mostly confined to its conus portion. The cardiogram

is also of some diagnostic value in that the partial bundle-branch block in the later examinations suggesting possible injury to the conducting system, points to the presence of the ventricular septal defect. That is to say, although in a number of recorded cases of ventricular septal defects these fibers have undoubtedly escaped and no interference with conduction has occurred, there are a sufficient number of others in which they have been definitely proved to have undergone deflection and interruption with resultant partial or complete congenital heart block. Of this the most classic illustration is the recent carefully investigated specimen reported by Wilson and Grant.⁷ The electrocardiogram may be taken therefore to be further evidence suggesting the presence of a defect of the interventricular septum, while the right predominance points to the presence of a complicating lesion leading to hypertrophy of the right heart which, since pulmonary stenosis could have been excluded (see above) one might well have concluded in the light of the symptomatology to be the dextroposition of the aorta that actually did exist.

An interesting phase was the terminal streptococcic cerebral abscess. There was no endocarditis, and no history nor source of infection from which a paradoxical embolism might be traced, but it is believed by us that some such focus was present. The collected cases³ make it clear that in the presence of brain symptoms in congenital heart cases, cerebral abscess should be considered, and the presence of cerebral symptoms in conjunction with signs of a cardiac abnormality may actually clinch the diagnosis of a cardiac septal defect.

Summary. 1. The combination known as the "Tetralogy of Fallot," namely, pulmonary stenosis, ventricular septal defect, dextroposition of the aorta and hypertrophy of the right ventricle, is the commonest of all cardiac abnormalities in cases of congenital cyanosis reaching adult life.

2. A case in a male adult observed during life with the help of Roentgen rays and electrocardiogram and confirmed by necropsy, is here presented. There was found a large interventricular septal defect with dextroposition of the aorta but without any pulmonary stenosis or hypoplasia. This differs, therefore, from the classic "tetralogy" in that the pulmonary conus, orifice and artery are normally developed and have undergone dilatation as a result of influx of blood from the left ventricle through the defect into the pulmonary circulation.

3. Such cases as this of pulmonary dilatation with ventricular septal defect and dextroposition of the aorta have been described by Abbott⁸ as of the Eisenmenger type, after the author who published the first case on record, and are relatively rare. Clinically, this condition is differentiated from the "tetralogy" by the more moderate degree of cyanosis and clubbing (as is evident from the

anatomic conditions which are more favorable for oxygenation), the localization over the precordium of a harsh systolic murmur generated at the defect and not transmitted into the vessels, the occasional presence (as in the present case) of a diastolic murmur of pulmonary insufficiency, and the distinctive character of the Roentgen ray picture which shows in cases with well-marked pulmonary dilatation as in the present one, a large pulmonary arc and increased hilum shadows, as well as a broadening of the aortic shadow to the right above the base (dextroposition), and a more moderate degree of right-sided enlargement than would occur in the "tetralogy." These features of the Roentgen ray are shown in the present case (Fig. 1) in exquisite pronouncement.

4. In the presence of the above complex the evidence supplied by the cardiogram, of interference with the conduction bundle is also of diagnostic value, as suggestive of an interventricular septal defect, such as actually existed here.

Termination by cerebral abscess is especially liable to occur in a ventricular septal defect with dextroposition, for this combination supplies a direct path for the transmission of a "crossed" embolus from a septic focus in the lesser circulation. Although this focus was not located in the present case, it nevertheless adds another to the series collected and recorded^{3,5,9,10} in which a lethal cerebral complication was associated with, and consequent upon, a cardiac septal defect.

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**FULMINATING MENINGOCOCCUS SEPTICEMIA WITHOUT
MENINGITIS.**

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THERE are two possible modes by which the meningococcus may reach the central nervous system from its original place of lodgment in the nasopharynx. The lymphatic route was formerly considered the more frequent, especially in view of the large number of negative blood cultures obtained by workers with cerebrospinal meningitis. More recently, however, and especially since the World War gave opportunities for extensive observation,¹ it has come to be recognized that a meningococcemia very frequently occurs before localization of the infection. Herrick² has laid much emphasis on this point, and finds in it the indication for early and vigorous intravenous therapy. By this means, he reports a considerable reduction in mortality, particularly under military conditions where patients come under observation before the clinical picture has fully evolved. Herrick found positive blood cultures in 45 per cent of his cases.

In every epidemic, meningococcus infections are observed which run their course without metastasis to the central nervous system, being septicemic in nature throughout. For this reason Herrick³ considers the expression "epidemic cerebrospinal meningitis" a misnomer, since it describes only one manifestation of a protean disease. He recommends that it be superseded by the terms "meningococcus infection" and "meningococcus meningitis."

Two forms of purely septic meningococcus infection occur:

1. A prolonged febrile state, characterized frequently by arthritic symptoms and a mild roseolar or petechial eruption. Prostration is often not severe. This form may resemble typhoid fever or malaria. Zinsser⁴ says of these patients: "We advise a serious consideration of the diagnosis of meningococcus septicemia whenever a prolonged case of fever with leukocytosis and a slight variable rash comes under observation."

2. Fulminating cases with widespread purpuric blotches. In these death may occur very rapidly. In fact, it has been reported as early as four hours after the onset of symptoms.

The following case of the latter type seems worth reporting, since it illustrates the extreme intensity which meningococcus septicemia may develop without localization in the central nervous system, which we are so prone to regard as the important feature of these infections:

Case Report. K. M., a Norwegian seaman, aged eighteen years, was admitted to the medical service of Dr. George W. Norris at Pennsylvania

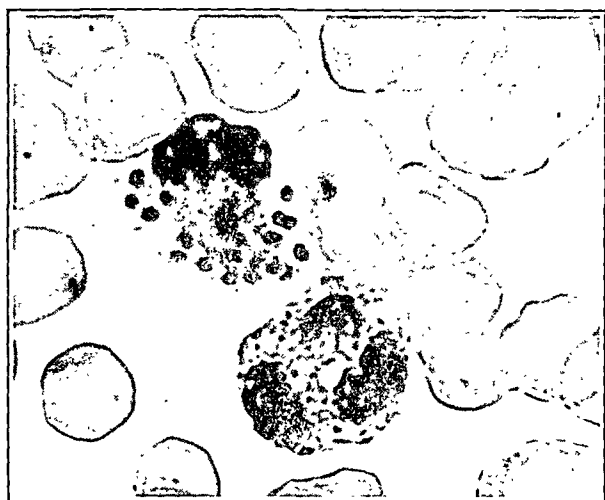


FIG. 1.



FIG. 2.

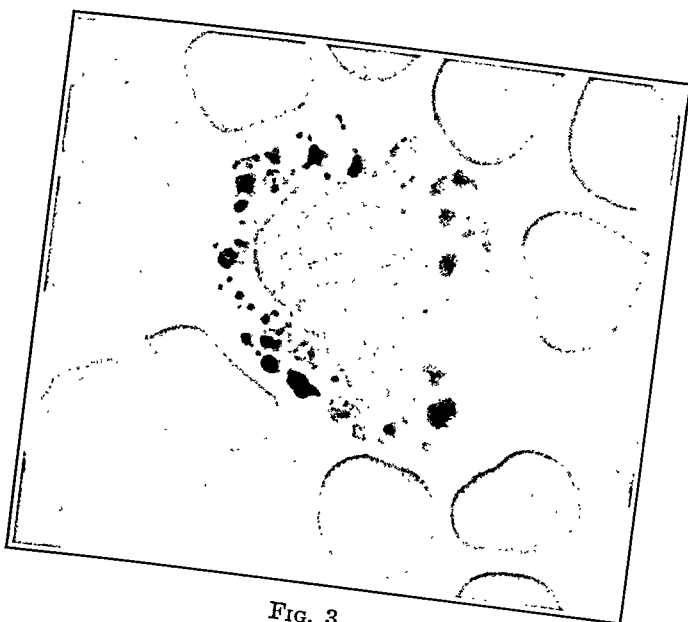


FIG. 3.



FIG. 4.

Hospital, March 23, 1928, at 10.30 P.M. He had been perfectly well until the morning of admission, when, about 9 A.M., he complained of headache. He had no chill, but felt feverish. He remained in bed all day and seemed somewhat stuporous. He vomited once in the late afternoon. In the evening, his uncle brought him to the hospital in a taxicab. On the way to the hospital, purple blotches were seen coming out over the patient's body. His skin had previously been clear.

The patient's past history was negative except for malaria, for which he had been treated four months previously in a hospital in Virginia. He was a seaman who had traveled widely in the Orient and Europe in the past two years. He had recently been employed on freight vessels going to the West Indies. He had been leading a quiet life visiting relatives in Philadelphia during the week preceding his illness.

On admission, the patient was delirious and very restless, tossing about in a semicoma from which he could be aroused to answer short questions. His skin was hot and dry, and covered everywhere with small and large irregular red blotches which did not disappear on pressure. These purpuric spots ranged from about 0.5 cm. to about 2 cm. in diameter. The pupils were small and did not react to light. There were many petechiæ in the conjunctivæ. The pharynx could not be well examined because of difficulty in managing the patient. There was slight stiffness of the neck. Examination of the lungs was negative. The heart rate was very rapid (160), but the sounds were of fair quality and no murmurs were heard. Blood pressure was 62 systolic and 50 diastolic. The abdomen was scaphoid, with no demonstrable tenderness or rigidity. Knee jerks could not be elicited. Kernig's sign was slightly positive; Babinski's negative.

Lumbar puncture was performed shortly after admission, a small amount of chloroform being required on account of the patient's struggling. Fifteen cubic centimeters of crystal-clear fluid were obtained. The pressure was 15 mm. of mercury, but the increase could be accounted for by the patient's movements. There were 12 cells per c.mm., but globulin was not increased (Pandy's Reagent). The colloidal-gold curve was later reported to be 0000000000.

A blood count made shortly after admission showed 4,170,000 red blood cells per c.mm. and 88,550 leukocytes, of which 64 per cent were polymorphonuclears, 22 per cent myelocytes, 10 per cent lymphocytes, 2 per cent large mononuclears and 2 per cent eosinophils. An ordinary cover-slip smear of the blood, stained with Wright's stain, revealed a large number of intracellular and extracellular diplococci, as shown in the accompanying photomicrographs. Single leukocytes containing as many as 30 pairs of cocci were observed. A similar blood smear stained by Gram's method—in which the red blood cells were dissolved, leaving large numbers of leukocytes loaded with diplococci—gave a picture closely resembling the smear from a fresh gonococcic urethritis. The organisms exhibited the marked variation in size which is so characteristic of the meningococcus.

The patient rapidly became completely comatose, with rapid, labored respirations and increasing cyanosis. The heart rate grew very rapid and the pulse almost imperceptible at the wrist. The suggestion of cervical rigidity did not develop into actual stiffness. The patient died at 12.40 A.M., March 24, 1928, about fifteen and a half hours after the onset of his illness.

A blood culture taken immediately after death yielded a vigorous growth of meningococci. These failed to agglutinate in type sera obtained from the Division of Laboratories and Research of the New York State Department of Health, but a good agglutination was obtained with polyvalent serum (Mulford). The organism thus belonged to a subsidiary strain. A blood chemistry taken within a few minutes of death gave the following values: Sugar, 30; urea nitrogen, 35; creatinine, 4.3 mg. per 100 cc.

Necropsy. The important necropsy findings were as follows: The body was that of a well-nourished and extraordinarily well-developed young white male. The skin was everywhere profusely covered with large, irregular purpuric blotches. Numerous petechiæ were seen on the conjunctivæ and on all visible mucous membranes. There was no free fluid in the abdominal or pleural cavities. All serous and mucosal surfaces of the abdominal and thoracic viscera were thickly studded with innumerable petechiæ. On section, the lungs were reddish-brown in color and bled freely, but no definite consolidation was noted. The mesenteric glands were all enlarged and Peyer's patches were markedly hyperplastic, but not ulcerated. The adrenals were enlarged, softened and hemorrhagic, being almost black throughout. Microscopic study revealed practically total destruction of adrenal tissue from massive hemorrhages.

On removing the calvarium, great engorgement of vessels and definite edema were noted over the cerebral convolutions. There was no evidence, however, of a purulent exudate over the hemispheres or at the base of the brain. A swab from the surface of the brain gave a sparse growth of meningococci in pure culture (autopsy not performed until thirty-five hours after death!).

The spinal cord was not examined.

Discussion. The remarkable feature of this case is the extreme intensity of the meningococcus septicemia. Although this is not the first time meningococci have been demonstrated in an ordinary blood smear, we are not aware that so many have been observed before. The mild cervical rigidity and slightly positive Kernig's sign suggested meningitis. The spinal-fluid findings, however, and later the necropsy, indicated that these signs were due merely to meningismus, which might occur in any similarly severe toxic process.

The strikingly low blood-sugar value and marked hypotension seem well accounted for by the bilateral hemorrhagic destruction of the adrenals discovered at necropsy. The total absence of adrenal secretion, with resulting failure of carbohydrate mobilization and vasomotor control may well have been the immediate cause of death.

It is unlikely that serum therapy could change the outcome of fulminating infections such as the one described. Such cases, nevertheless, serve to emphasize the importance of bacteremia as a feature of meningococcus infections, and indicate the desirability of vigorous intravenous therapy even when localization of the infection in the meninges seems to have occurred.

Conclusions. Meningococcus meningitis is frequently, and we believe usually, preceded by meningococcus bacteremia. Fulminating infections with this organism may occur and cause death within a few hours after the onset of symptoms, the only clinical and anatomic findings being those of an intense septicemia. Such a case is here described.

Vigorous intravenous therapy should never be omitted in treating meningococcus infections.

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LEUKOSARCOMA.

WITH REPORT OF A CASE BEGINNING WITH A PRIMARY RETRO-
PERITONEAL LYMPHOSARCOMA AND TERMINATING WITH
LEUKEMIA.*

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ALL degrees of lymphoid hyperplasia are illustrated in various types of disease of lymphoid tissue. At one end of the scale are the benign hyperplasias, and at the other end, the atypical and invasive lymphosarcomas. Between these are the cases of typical lymphatic leukemia, which show a generalized hyperplasia of the lymphoid tissue and a lymphemia. They usually have only slightly atypical cells and lack the highly invasive character of lymphosarcoma. Intermediate between this group and the lymphosarcomas are the cases to which Sternberg has applied the term leukosarcoma.^{1,2,3} These cases are characterized essentially by the combination of a more or less localized, primary, and invasive lymphoid tumor and a leukemic blood picture.

A survey of the literature that we have made reveals at least 107 cases which appear to come in this group. The probable primary site of the invasive tumor is as follows: Mediastinum, 60; skin, 11; eye and eyelids, 11; retroperitoneal and abdominal lymph nodes, 6; pleura and peritoneum, 2; femur, 2; breast, 2; dura, 2; intestines, 2; axillary lymph nodes, 1; skull, 1; cervical lymph nodes, 1; lymph nodes generally, 1; ribs, 1; cervix of uterus, 1; ovaries, 1; tonsils, 1; prostate, 1.

In at least 16 cases, various observers have noted early in the disease the presence of lymphoid enlargements without blood involvement, and subsequently a leukemic blood picture (⁴⁻¹⁶). Of interest in this connection are 9 cases in which there was a similar story, but no invasive tumors (¹⁷⁻²⁵). These cases suggest that in many other cases of leukemia there was an earlier local process which later was also manifest in the blood, producing leukemia. The case that we are reporting points toward this course of the disease.

* Presented before the Philadelphia Pathological Society, October 11, 1928.

Case Report. The patient, Edward B., white, aged sixty years, in July, 1926, noticed a swelling in the right inguinal region. This gradually increased in size and in March, 1927, lymphedema of the right leg and genitalia developed. He was admitted to the surgical division of the University Hospital on July 2, 1927, when a lymph node was removed from the inguinal region. The pathologic diagnosis by Dr. A. E. Bothe was lymphosarcoma. Roentgen ray examination on July 1, 1927, was negative for mediastinal glands, but showed in the pelvis a large mass which did not appear to be springing from the bone. Physical examination showed a general lymphadenopathy due to a moderate number of discrete, soft, nontender lymph nodes, from 0.5 to 2 cm. in diameter, and a large firm mass in the pelvis. The leukocyte count at this time was 7300 cells per c.mm. The patient was referred to Dr. Henry Pancoast for Roentgen ray therapy and was treated three times a week from July 12, 1927, to November 17, 1927. While he was under this treatment, numerous leukocyte counts were made, ranging between 5000 and 7000 per c.mm. The differential count showed 50 to 60 per cent neutrophils, 30 to 40 per cent lymphocytes, 3 to 10 per cent large mononuclear cells, and 2 to 3 per cent eosinophils. The percentage of neutrophils gradually diminished, and that of lymphocytes gradually increased. The erythrocytes ranged between 3,500,000 and 4,000,000 per c.mm. and the hemoglobin between 72 and 85 per cent. In September the mass in the abdomen was noted to be much smaller and the patient felt better.

About November 1, 1927, the patient developed a gradually increasing jaundice, and began to complain of weakness, anorexia, nausea, and palpitation. On November 10, 1927, the leukocyte count was noted to be 96,000 and on November 17, 1927, it was 100,000 per c.mm. The differential count showed 90 per cent small lymphocytes.

On November 21, 1927, he was admitted to the medical division of the University Hospital on the service of Dr. Alfred Stengel. The outstanding findings on physical examination were a vaguely defined, deep-seated mass in the right side of the abdomen, moderate jaundice, generalized adenopathy, signs of fluid in the right chest and marked enlargement of the liver. The spleen was not palpable. The blood count in November 22, 1927, was as follows: Red blood cells, 2,960,000; hemoglobin, 59 per cent; white blood cells, 96,000, and a differential count of small lymphocytes, 97 per cent; neutrophils, 2 per cent, and large mononuclear cells, 1 per cent. The Wassermann reaction was negative.

At this time the clinical diagnosis of leukosarcoma was made although the site of the primary invasive tumor was not definitely known. It was assumed, however, because of the Roentgen ray examination on July 1, 1927, which showed a large mass in the pelvis, that it had its origin in the retroperitoneal lymph nodes.

On December 1, 1927, the leukocyte count had risen to 288,000 with 96 per cent small lymphocytes, and on December 3, 1927, a few hours before death, the leukocyte count was 444,000. The average temperature was 100, the average pulse 100, and the average respiration 23.

Surgical Specimen. (Inguinal lymph node removed July 2, 1927.) The gross specimen was noted as being part of a lymph node 2.5 by 2.5 by 2 cm. On section it was light pink in color, with pin-point hemorrhagic areas. The capsule was noted as being in places 2 mm. in thickness.

Microscopic Examination. Throughout the node, there is an irregular alternation of lighter staining areas with darker areas (Fig. 1). The darker zones contain chiefly small lymphoid cells, while the lighter zones contain many larger cells which stain less intensely, show numerous mitotic figures, and are less compactly arranged. In places the lighter portions are round, resembling germinal centers. The sinuses and original architecture have



FIG. 1.—Section through a lymph node showing the tendency to form the lighter and darker areas of the tumor. Mag. 10 \times .

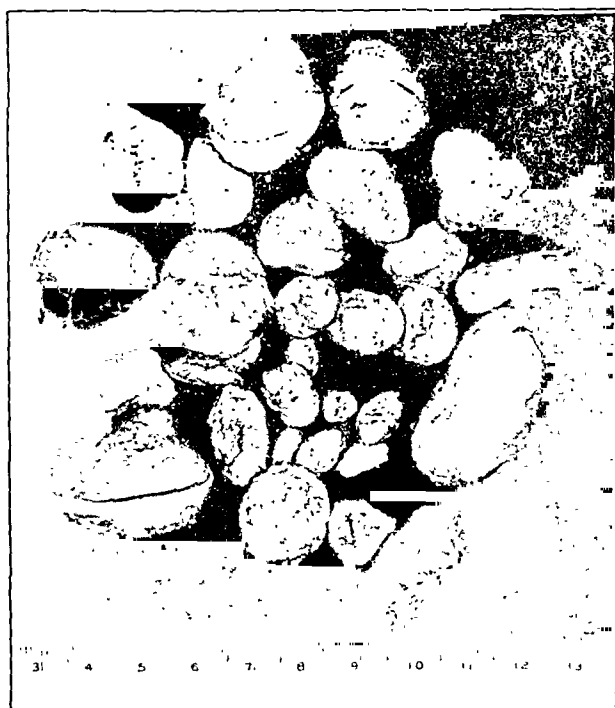


FIG. 2.—A group of lymph nodes from the right axilla. The loosely attached, uninvaded fat was dissected away, leaving very discrete nodes. Compare with Fig. 3.

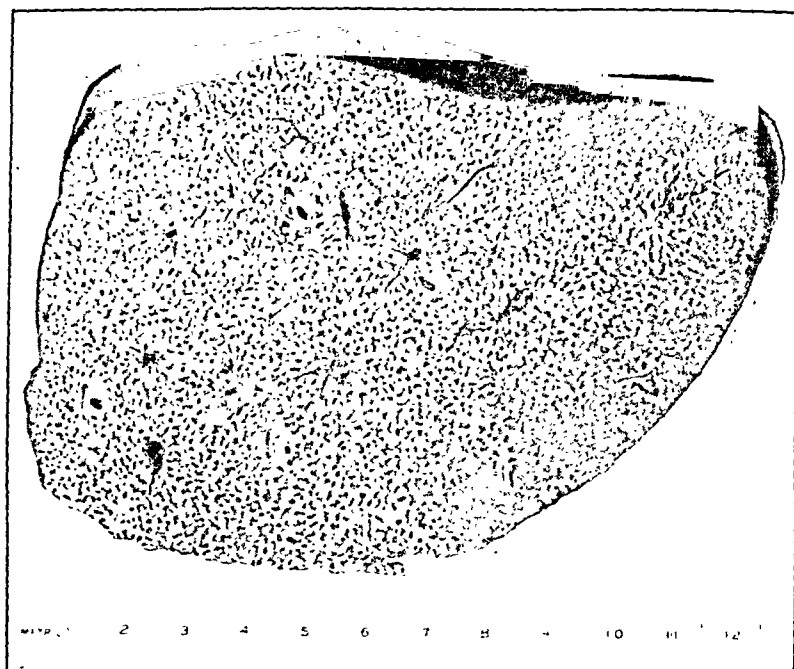


FIG. 4.—A section of the cut surface of the liver, showing the uniform tumor infiltration in the portal areas.

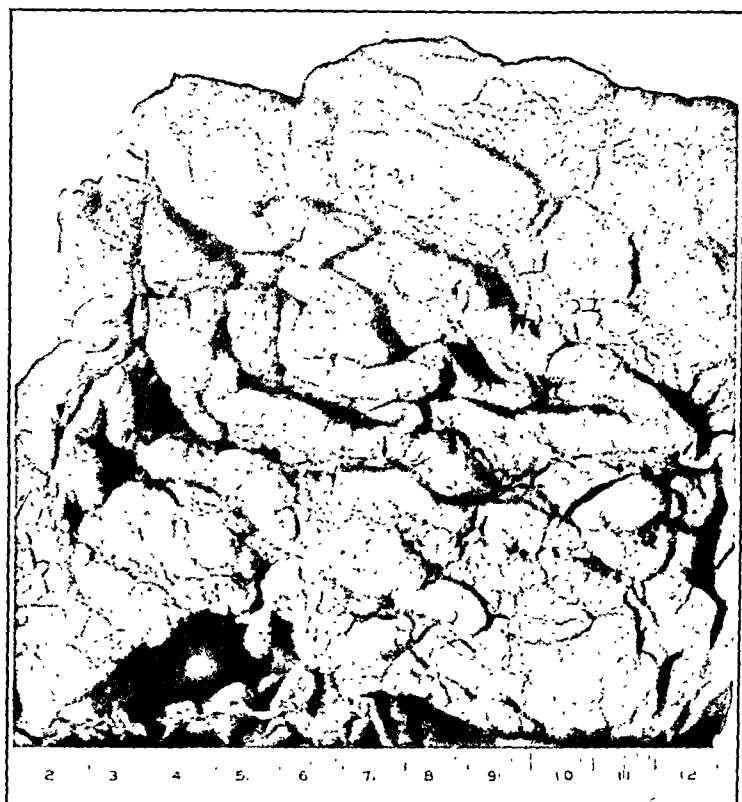


FIG. 6.—Stomach, showing the diffuse tumor involvement of the mucosa and submucosa. At one side of the picture a cut surface is shown.

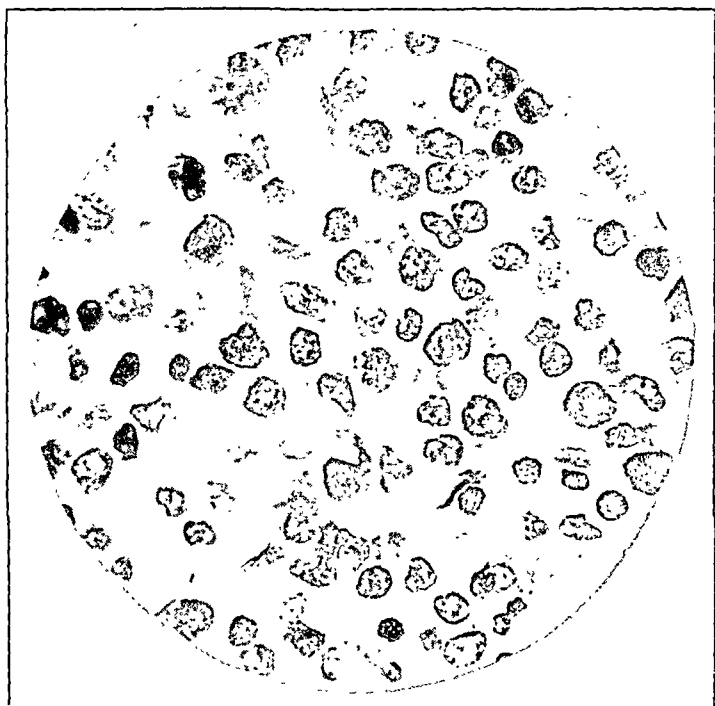


FIG. 7.—The large tumor cells in the portal areas of the liver. Mag. 650 X.

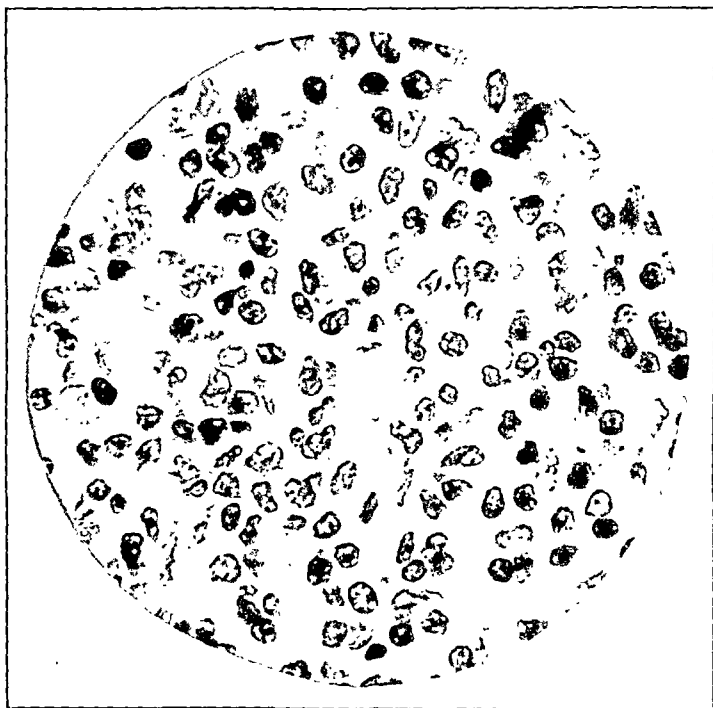


FIG. 8.—The small tumor lymphoid cells in a lymph node. Compare with Fig. 7. Mag. 650 X.

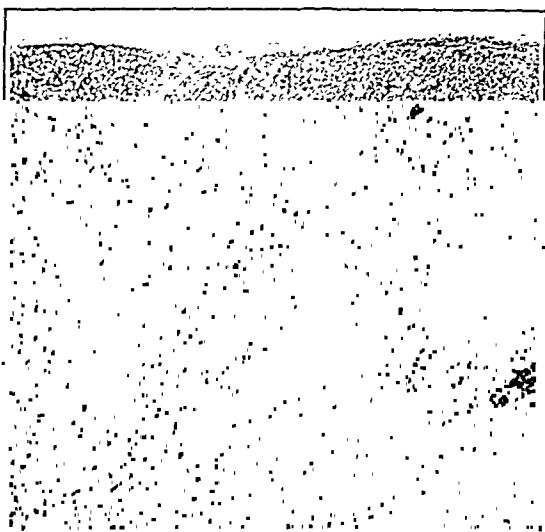


FIG. 9.—The tumor nodule in the kidney, showing the alternation of the lighter and darker zones of the tumor. The section is at the margin of the tumor and the adjacent kidney tissue. Mag. 10 \times .

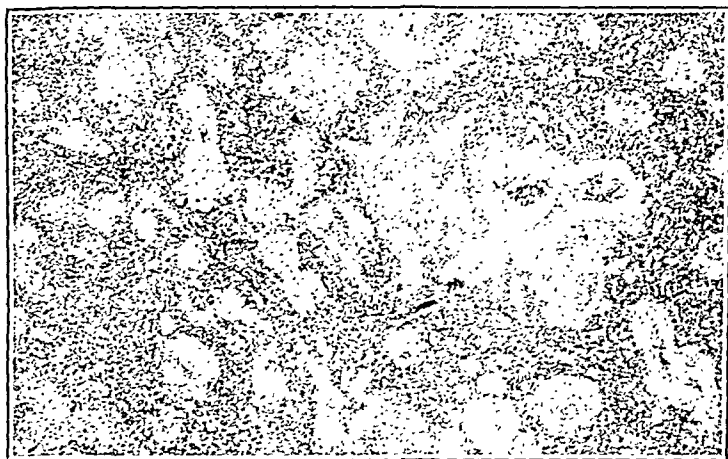


FIG. 10.—Spleen. This shows the tendency of the tumor to form more or less round lighter areas surrounded by darker areas. Mag. 10 \times .

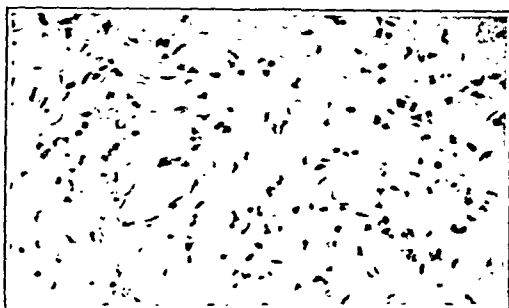


FIG. 11.—A retroperitoneal lymph node affected by the Roentgen rays, showing the marked diminution of lymphoid cells and increase of the fibrous stroma. Mag. 170 \times .

been replaced by tumor. There is marked infiltration of the tumor from 1 to 2 mm. beyond the original capsule, which in places has been replaced by the neoplasm. The lymphoid cells outside the capsule are less densely compact than those in the node. The cells have the same characters as in the tumor tissue found at autopsy and will be described later.

Autopsy Findings. The autopsy was performed on December 3, 1927, two hours postmortem, by Dr. D. H. Flashman.

Chief Diagnoses. Leukosarcomatosis, with primary lymphosarcoma of the retroperitoneal lymph nodes, and metastases to inguinal, mesenteric, gastric, mediastinal, axillary and cervical lymph nodes; heart; lungs; liver; spleen; kidneys; ureters; prostate; gall bladder; pancreas; suprarenal glands; stomach; duodenum; bone marrow of the right femur; thyroid; and blood (lymphatic leukemia). Lungs: Emphysema, atelectasis and healed apical tuberculosis. Liver, kidney, pancreas and suprarenals: Parenchymatous degeneration. Bone marrow of right tibia and lumbar vertebrae: Hyperplasia. Kidneys: Right—hydronephrosis, and chronic focal glomerulonephritis; left—hypertrophy.

Anatomical Description. The body is that of a well-developed, moderately emaciated white man, aged sixty years, and 172 cm. in length. *Skin:* There is a faint yellowish tinge generally, suggestive of slight jaundice. A few petechiae are present beneath the left clavicle. Over the lower abdomen and upper part of the thighs there is a brownish pigmentation, probably from the Roentgen ray exposures. *Eyes:* The sclerae have a faint yellowish tint. *Mouth:* There are a few teeth missing and marked pyorrhea. *Peripheral lymph nodes:* On the left side of the neck above the clavicle there are felt 4 discrete glands 1 cm. in diameter. In the right axilla there are felt numerous discrete glands from 0.5 to 2 cm. in diameter, in all making a mass about 8 cm. in diameter. A few small nodes are felt in both inguinal and femoral regions in addition to a diffuse firm thickening.

Internal Examination. The subcutaneous fat is markedly atrophied. In the right axilla the lymph nodes are dissected out. There are about 30 nodes, from 0.5 to 2 cm. in diameter, all similar, discrete, and slightly firm (Fig. 2). Generally there is no appreciable invasion of the surrounding tissue, but in a few small areas there is slight invasion of the adjacent fat. The cut surface is slightly bulging, grayish-white, with small yellowish areas of necrosis in places, slightly soft, smooth or slightly granular, and moist. In the right inguinal and femoral regions there are about 8 lymph nodes from 0.5 to 1 cm. in diameter, surrounded by a diffuse infiltration of the tumor into the connective tissue, which appears quite fibrous. These nodes are much firmer than the axillary nodes and the cut surface is firm, slightly rough, fibrous, grayish-white, and not bulging. The fibrosis seems to be an effect of the Roentgen rays, since this region received the greatest exposure. A few similar but slightly larger nodes are also present in the left inguinal and femoral regions, and these do not show as much fibrosis as on the other side.

Bone Marrow. That of the right femur is examined for a length of 3 cm. at the midportion. It is uniformly grayish-white, soft, shiny and without fat. The marrow of the right tibia is yellowish and fatty for the most part, with portions slightly reddish, suggestive of red-cell hyperplasia; that of the lumbar vertebrae is moderately red.

Abdominal Cavity. The liver edge extends about 10 cm. below the costal margin. The diaphragm extends up on both sides to the third intercostal space. The posterior and lateral two-thirds of the spleen are firmly adherent to the chest wall, and the lower edge is 2 cm. above the costal margin. The mesentery shows throughout enlarged lymph nodes from 1 to 2 cm. in diameter, all discrete, firm, well encapsulated, and similar to those of the right axilla. All around the pancreas there are about 20 nodes of similar

character from 1 to 3 cm. in diameter. Beneath the peritoneal lining of the pelvis there is a diffuse uniform thickening of the posterior retroperitoneal tissues, averaging 2 to 3 cm. in thickness. It is most marked laterally, extending over the brim of the pelvis toward both groins, especially along the right femoral artery and vein. Except for a small plaque 5 mm. in diameter and 1 mm. thick, the peritoneal surface is perfectly smooth. Superficially the involvement of this tissue is not recognizable, but on incision the thickening is made out. This is composed of lymph nodes replaced by a firm, white, smooth, moist tumor tissue which infiltrates diffusely the surrounding connective tissue, where the tumor can be distinguished by its more opaque, pearly white, shiny appearance. These tumor areas are firmly adherent to the adjacent bone, connective tissue, muscle, and other



FIG. 3.—Cross-sections of the retroperitoneal tumor in the region of the aorta showing the firm nodes embedded in the diffuse infiltration of tumor.

structures. This involvement extends up over the vertebræ toward the diaphragm, varying in thickness about the aorta from 2 to 3 cm. laterally and about 1 cm. anteriorly and posteriorly (Fig. 3). In the region over the lower lumbar vertebræ and across the pelvis, the vena cava and iliac vessels are completely embedded in tumor which compresses and slightly infiltrates the wall of the veins, and in places small, whitish, firm thickenings of the intima are made out. When traced upward from the pelvic region the retroperitoneal lymph nodes along the vertebræ appear more and more discrete and there is less infiltration of the connective tissue about them. Both ureters are involved, more marked on the right and toward the kidney and bladder. They are surrounded by tumor tissue which infiltrates the wall and narrows the lumen, but does not project into the lumen, except for shallow plaques near the pelvis of the right kidney. The left suprarenal is firmly adherent at one pole to tumor tissue invading it from the retroperitoneal mass. It appears that the primary source of the tumor is in the retroperitoneal tissue in the region of the pelvis and in the right groin. Here

it has marked invasive tendency, but farther up, it gradually loses its local invasiveness and spreads extensively through the lymphatic system.

Pleural Cavity. There are a few slight adhesions at the left apex.

Mediastinum. There are about 4 nodes, 1 to 1.5 cm. in diameter, similar to those in the axilla. The thymic tissue is involuted and grossly free from tumor.

Pericardial Cavity. The heart is displaced slightly to the left, the right border being at the midline. Apparently this is due to the upward pressure of the liver. The pericardium over the aorta just above its origin shows tumor involvement, appearing as a pearly white, firm plaque about 4 cm. in diameter, 3 mm. thick in the center, and thinning out toward its irregular, indefinite margin.

Heart. It weighs 320 gm. It is essentially negative.

Lungs. The right lung weighs 400 gm. The left lung weighs 340 gm. They are slightly emphysematous, and in places at the bases slightly atelectatic. At the left apex there is a slightly retracted, fibrous scarring. The bronchial lymph nodes and the lung are not grossly involved with tumor.

Liver. It weighs 4570 gm. It is markedly enlarged, with rounded edges, and of slightly soft consistency. The external surface has a uniformly mottled appearance, with opaque, pearly white granules corresponding with the lobules. Near the midinferior border of the liver, the capsule has a patch of similar tumor tissue 1 to 2 cm. in diameter and 0.5 mm. thick. The ligaments of the liver show tumor infiltration. On section, the liver cuts with increased resistance. The cut surface is slightly rough with enlarged lobules throughout. Corresponding to the portal zones of the lobules there is a grayish-white, interlacing tumor infiltration. The central portions are reddish-brown. The connective tissue about the larger veins and ducts shows a diffuse, white tumor invasion for a width of 0.5 to 1 cm. (Fig. 4). The capsule of the liver over the gall bladder shows a dense tumor infiltration about 0.5 to 1 cm. in thickness, firmly adhering the gall bladder to the liver.

Gall Bladder. It is moderately distended with a thick black bile. The wall is infiltrated in patches 1 to 2 cm. in diameter and about 0.5 to 1 cm. in thickness. The mucosa is in places slightly rough and there are several shallow patches of polypoid projections of the mucosa overlying the areas involved with tumor. A few nodes similar to those in the mesentery are present about the hilus of the liver. The portal vein is negative.

Spleen. It weighs 830 gm., is markedly enlarged and of firm consistency. On the lateral surface there is a hyaline plaque of irregular shape about 7 cm. in diameter and 1 to 2 mm. in thickness. The capsule is thickened generally. On section the lymph nodules appear markedly enlarged throughout, and opaque, white granules of tumor can be made out generally. The cut surface is firm, smooth and moderately red. Streaks of fibrous tissue 1 to 2 cm. long and perpendicular to the surface are present beneath the hyaline plaque.

Pancreas. On the surface and in its substance there are numerous irregular pearly white, firm zones of tumor infiltration from 0.5 to 1.5 cm. in diameter (Fig. 5).

Suprarenals. Together they weight 8 to 9 gm. They are similar, having a narrow, deeply yellow cortex and a normal medulla. The surface of the left gland is invaded at one point by tumor from the surrounding tissues.

Kidneys and Ureters. The right kidney weighs 130 gm. It is of slightly increased resistance. The capsule strips readily leaving a slightly granular surface. On section, it cuts with increased resistance. The cortex in places is slightly narrowed, and the striations are quite irregular and indefinite. The medulla shows a few areas with yellowish amorphous precipitate. The pelvis is moderately distended and filled with abundant

similar precipitate. The lumen of the ureter in the first 5 to 6 cm. is markedly narrowed by the tumor involvement of the wall. The tissue about the pelvis shows a diffuse tumor involvement surrounding the vessels (Fig. 5). The left kidney weighs 240 gm. The cortex is 8 mm. wide. At one point in the cortex there is a white tumor nodule 2 cm. in diameter (Fig. 5). A few tiny opaque whitish dots suggestive of tumor are present in the cortex. The left ureter is not constricted as much as on the other side, but at the region just proximal to the bladder for a length of 2 cm. there is a marked accumulation of amorphous yellowish precipitate, some of which is embedded superficially in the lining.

Gastrointestinal Tract. The mucosa of the stomach (Fig. 6) shows markedly thickened folds and irregular projections throughout. On section there is diffuse, white tumor tissue infiltrating the submucosa chiefly, but in places also the mucosa and muscularis. The tumor areas are in places 1.5 cm. in thickness. There is some congestion and there are a few petechial hemorrhages, but no ulceration of the mucosa. In the duodenum and first

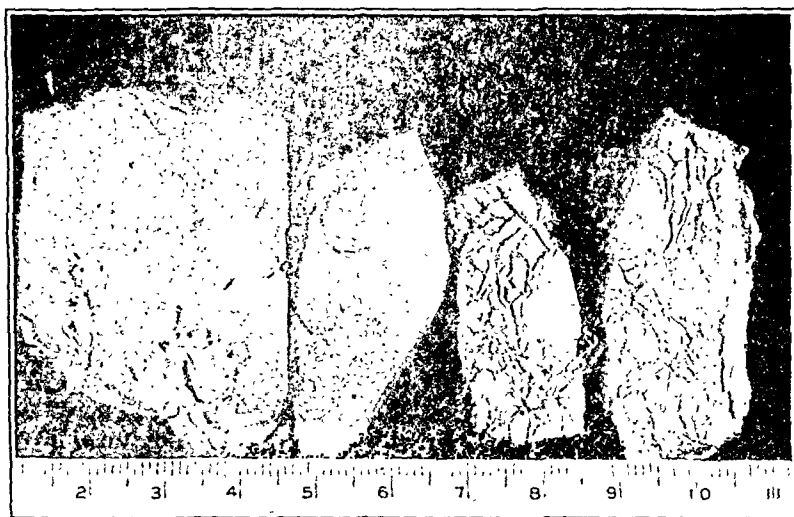


FIG. 5.—The larger piece of the kidney shows diffuse tumor infiltration in the region of the pelvic fat. The smaller piece of the kidney shows the circumscribed nodule found in the left kidney. The other two pieces show nodules of tumor in the pancreas.

portion of the jejunum, there are found in the submucosa small, similar tumor areas from 2 to 5 mm. in diameter. The remaining portion of the gastrointestinal tract is negative.

Pelvic Organs. The bladder wall is hypertrophied, but not involved by the neoplasm. The prostate is slightly enlarged, of normal consistency, and on section there are a few 0.5 cm. areas of hypertrophy with dilated glands. No tumor involvement is made out grossly.

Thyroid. It is not enlarged and a small piece is removed. It shows slight fibrosis, but no gross tumor.

Aorta. The lumen is slightly dilated and the wall is slightly thickened. Just above the aortic valve there is a whitish, shallow, atheromatous plaque about 1 cm. in diameter. A small amount of yellowish atheromata are scattered generally, more marked in the lumbar region where there are a few small ulcerated areas. Calcification is very slight in a few areas.

The brain and cord are not obtained.

Microscopic Findings. The tissue was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin.

In the prostate, thyroid, heart, and lung small tumor areas are found which were not recognized grossly. Tumor areas are present in the sections of all the other organs where they were noted grossly.

In addition to the presence of the tumor the following changes are present in the sections of the various organs: The *heart* shows an occasional focus of fibrosis in the muscle and slight fibrous thickening of the intima of the coronary artery. In the *lung* are areas of atelectasis and of emphysema. The *liver* cells have some variation in the size of the nuclei and a uniform, finely vacuolar, swollen cytoplasm characteristic of hydropic degeneration and cloudy swelling. The liver cells adjacent to the tumor areas show compression atrophy. The epithelium of the bile ducts is hypertrophied. The cells in the central zones have slight pigment deposition and atrophy. In the *spleen* there is the thick hyaline capsule noted grossly, and beneath this there are areas of a rather loose fibrous structure and areas of hemorrhage. Slight hyaline degeneration of the arterioles is present. In the *left kidney* there is generally cloudy swelling and hydropic degeneration. An occasional fibrosed glomerulus surrounded by slight fibrosis and lymphoid cell infiltration is present, especially near the surface. There is atrophy of collecting tubules of the medulla and a rare hyaline cast. The *right kidney* shows near the surface many fibrosed glomeruli, surrounded by areas with atrophied tubules, fibrosis, and slight lymphoid cell infiltration. Similar but more marked degenerative changes are present as in the other kidney. The changes seem to be due to the hydronephrosis, since the medulla and collecting tubules show the greater amount of degeneration. The epithelium of the *ureter* is hyperplastic and hypertrophied, and the muscular wall is thickened. In the *pancreas* some of the islands of Langerhans have moderate hyperplasia and the cytoplasm of the acinal cells shows vacuolar degeneration. In the *thyroid* there is slight hyperplasia of the epithelial cells and in places tumor invasion is present between the follicles, compressing and replacing them. The *aorta* has in places a thickened intima with fatty material, fibrosis, and slight calcification. The media in places shows hyaline change and atrophy of cells. Very slight perivascular infiltration of lymphocytes with occasional plasma cells are found in the adventitia. The *bone marrow of the tibia* has in places marked hyperplasia due chiefly to red-cell formation; that of the femur shows only tumor.

Character of the Tumor. The tumor for the most part displays two main types of areas, those with chiefly large cells and those with chiefly small cells, but there occur many irregular variations of size and arrangement.

The tumor in the portal zones of the liver lobules serves as an example of the areas with larger cells (Fig. 7). Here the larger cells, which correspond to lymphoblasts, are found in greatest numbers. The nuclei average 5.8μ in diameter and show numerous, usually atypical, mitotic figures. Rarely, several small nuclei are present in one cell. Compared with the small cells, the larger cells have a larger, less hyperchromatic, and more regular nucleus, a larger cytoplasm, and a less compact arrangement. Among these cells there are a few cells of the smaller type and of transitional types. In general both types appear to be more hyperchromatic than normal cells, and there is marked variation in size, shape and staining. Some of the nuclei have 1 to 3 large, basophilic nucleoli. A few karyorrhectic nuclei are present. The cytoplasm of the larger cells is small in amount, irregular in outline, finely vacuolar or granular, and acidophilic or basophilic. In some cells an eosinophilic, round body is present in the cytoplasm. Similar bodies, which seem to be of a degenerative nature, are also present between the cells. No evidence of a fibrous stroma formation is made out, but there is a fleecy, fibrinous exudate between the cells. An occasional red blood corpuscle and a rare eosinophil are present. A

few bile ducts with hypertrophied cells with vacuolar cytoplasm persist among the tumor cells. At the periphery of these tumor areas there is marked invasion of the adjacent sinusoids.

In the central portion of the liver lobules, away from the tumor areas, there is present in the sinusoids a marked increase in lymphoid cells similar to those in the vessels generally. These cells are smaller, more deeply staining, with very little cytoplasm, with irregular-shaped nucleus, and without mitotic figures. They resemble, but are not identical to, small lymphocytes. The average diameter of the nuclei of these cells is $4.4\ \mu$. The average diameter of normal lymphocytes in the tissues of a control case where the tissues were treated by the same technical processes is $4.3\ \mu$. The red blood corpuscles in the sections average $4.7\ \mu$. The proportion of tumor cells to red blood corpuscles in the capillaries is 1 to 3. The irregularity of the nucleus is most apparent on focusing up and down with the microscope. It does not seem to be due to shrinkage alone, as the other cells in the same sections do not have this character.

In the lymph nodes which have not been affected by the Roentgen rays, as in the original surgical specimen and the hyperplastic nodes of the axilla and other places, as well as in the nodule in the left kidney and in the spleen, the tumor shows a rather characteristic alternation of areas of large cells and small cells. This alternation often has a follicular arrangement with the larger cells in the center, corresponding to the appearance of germinal centers of normal lymph nodes (Figs. 1, 9 and 10). The larger cells resemble those in the tumor in the portal areas of the liver, while the smaller cells resemble those in the vessels generally (Fig. 8). This tendency to form follicular arrangements is not present in the sections of the bone marrow of the right femur, liver, gall bladder, stomach, lymph nodes only partially involved by tumor, and other places.

In those portions of lymph nodes and the spleen that are involved by the neoplasm there is obliteration of sinuses and normal landmarks. Infiltration beyond the capsule is more marked in the original surgical lymph node and the nodes of the retroperitoneal region than in the nodes which were more discrete grossly. The cells present in the diffusely invaded connective tissue and fat of the retroperitoneal region are in most sections chiefly the small and intermediate cells, mixed with a few cells of the larger type and here and there irregular foci of larger cells. In some sections the areas of large cells predominate.

The arrangement and combinations of these cells are very variable in different places. In the bone marrow of the femur the large type predominates with a few intermediate and smaller cells mixed among them. In the sections of the pancreas, stomach, and duodenum the cells are chiefly of the intermediate type. In the thyroid, lung, gall bladder, suprarenal, and prostate the large cell predominates. In the spleen the pulp spaces between the sinuses are filled with the small type of cell, suggesting that here is an important source of the small cells for the blood stream. Infiltration of vessels is also definitely taking place in the liver, bone marrow, and lymph nodes. In some lymph nodes the follicular areas of larger cells are composed of cells of an intermediate type. Mixed with the small tumor cells there are also some apparently normal lymphocytes, which are most numerous in the nodes that are least involved by tumor.

In areas of early involvement by the tumor a few mononuclear phagocytes and normal appearing lymphocytes are present and these are more numerous in areas of fat. Their presence seems best explained by the destruction of preëxisting tissue by the tumor. In the kidney there are small foci of small lymphoid cells about vessels and fibrosed glomeruli. Some of these lymphocytes appear normal, others appear like small tumor cells, and a few resemble the larger tumor cell. In lymph nodes with incomplete involvement por-

tions still show the preservation of the sinuses, which contain chiefly small tumor cells with a few larger ones, numerous mononuclear phagocytes, a few red cells, and some normal appearing lymphocytes. Some of the phagocytes contain from 1 to 3 well preserved, small tumor cells.

The tumor cells usually do not invade the media of large vessels, but in some of the iliac veins the infiltration extends through the intima. In one artery in the retroperitoneal tissue the vessel is invaded and thrombosed, with organization and canalization.

At one point in one of the retroperitoneal nodes there is an area of necrosis 3 mm. diameter. This appears to be in a focus of larger cells. The central portion shows some caseous necrosis. At the margin of this there are numerous mononuclear phagocytes and proliferating fibroblasts. In places there are groups of karyorrhectic necrotic cells, some of which appear to be large tumor cells and others phagocytes. Around the margin of these areas there are groups of large tumor cells which have not yet become necrotic mixed with others which have and some mononuclear phagocytes. The phagocytes in places resemble epithelioid cells, but there is no evidence of tuberculosis.

The retroperitoneal tissues, including the lymph nodes, ureters, veins, and prostate, show varying degrees of fibrosis and diminution of lymphocytes, apparently brought about by the Roentgen rays (Fig. 11). In some places there is no definite evidence of tumor, there remaining only connective tissue with scattered lymphocytes, most of which appear normal and tend to be smaller, darker, and more regular than those in the vessels. The average diameter of the nuclei of these cells is 3.4μ . In places foci of large or small cells still persist in varying degrees. The endothelial and connective tissue cells in these areas appear hypertrophied.

Discussion.—The autopsy presents a picture combining characters of lymphatic leukemia and lymphosarcoma and constituting a single type of involvement of intermediate character rather than a coincidence of two separate types. The involvement of the retroperitoneal tissues of the lower abdomen, pelvis and groins has the local infiltrative character of a lymphosarcoma, and appears to be an older lesion, as indicated by the more massive involvement and the clinical history. The more recent type of involvement of the lymph nodes elsewhere and of the liver, spleen, bone marrow, stomach and blood approaches, but does not attain the character of, a chronic lymphatic leukemia. The older and more recent types of lymph node involvement resemble each other in the presence of areas of large cells and of small cells in a rather characteristic formation. The older type, however, shows more invasion of the surrounding tissue. One can trace a gradual transition in the character of the lymphoid involvement in the retroperitoneal region along the lumbar vertebrae. Here there is a gradual loss of the infiltrative character of the tumor about the lymph nodes, going from the region of the pelvis toward the diaphragm. The circumscribed infiltrating processes in various organs, such as the kidney, pancreas, thyroid and prostate, appear like metastases of a lymphosarcoma, while the involvement of the liver, spleen, bone marrow and stomach approaches in character the diffuse distribution of a leukemia, but tends to retain the invasiveness of a lymphosarcoma. The involve-

ment of the lymphoid system is not universal as in typical lymphatic leukemia, but is much more extensive than in typical lymphosarcoma. The presence in the tissues of groups of large cells mixed with groups of small cells is likewise an intermediate characteristic in that it shows side by side two grades of differentiation of the tumor.

In the tissues there are both large and small tumor cells while in the blood practically only the small cell is found. Naturally, the small cell could more readily get into the vessels. However, the sections of the liver, lymph nodes, spleen and bone marrow show evidence of extensive invasion of bloodvessels not only by the smaller tumor cells but also by the larger cells. The relative absence of the larger cell in the blood suggests that in this case the larger cell tends to differentiate into a small cell in the blood stream. To be sure, many cases have been reported where the large cell is present both in the tissues and in the blood. But in this case, in the tissues the larger cells tend to differentiate into the small cell. This is shown by the presence of transitional forms and by the follicular arrangement of larger cells in the central portions surrounded by smaller cells, corresponding to the picture of a germinal center of a normal lymph node, where apparently the proliferating lymphoblasts differentiate to form the smaller lymphocytes which surround the germinal center and do not show evidence of division.

In 5 cases reported in the literature,^{13,14,15} as in our own case, the development of the leukemia happened to follow Roentgen ray treatment. The rays in all of these cases apparently had a marked beneficial effect locally. In our case it produced clinically a marked diminution in the size of the glands, and histologically in places almost complete replacement of the tumor cells by a fibrous stroma. However, it apparently had no preventive effect on the development of metastases or of the leukemia. Evans and Leucutia¹⁵ suggest that many cases of lymphosarcoma would develop leukemia if they lived long enough, as when life is prolonged by the Roentgen ray therapy.

Sternberg emphasized that the large lymphoblastic type of cell, which does not contain granules giving a positive oxidase reaction, was associated with his cases, and he believed this cell to be essential in these cases. In most cases of this type that have been reported, the large cell was present. In several cases of this type, however, the small cell predominated in the tissues and in the blood.^{16,27-33} In other cases there were areas of large and of small cells in the tissues, and large cells in the blood.^{10,12,16,26,34} In a few cases, as in our case, there were small cells in the blood and areas of large and of small cells in the tissues.^{35,36,37} In a case reported by Graetz³¹ in the tissues there were chiefly small cells, while in the blood early in the disease there were chiefly small cells and later chiefly large cells. It follows from this, as many observers have pointed out, that the term leukosarcoma cannot be restricted to cases having only large cells.

Similar combinations of local invasive tumors and leukemia occur in cases of myelogenous leukemia and especially in cases of chloroma, and for these Sternberg prefers to apply the term myeloleukosarcoma and chloromyeloleukosarcoma. Also there are cases which combine local tumors with aleukemic leukemias.

Objection has been made to this classification of tumors by Türk,³⁸ Herxheimer,⁴¹ Fraenkel,⁴² Herz,⁴⁰ Graetz,³¹ and others. The discussion depends chiefly on whether this classification is a separate entity or simply a manifestation of infiltration of a leukemic process. In our opinion the arguments that have been presented are based on different points of view and too finely drawn distinctions. There have been reported all transitions between lymphosarcoma and lymphatic leukemia, so that it is obvious from the material available that no sharp line can be drawn between them, except for purposes of convenience. From this point of view, however, there is a class of cases which are intermediate in character between typical lymphosarcoma and lymphatic leukemia, and for these the term leukosarcoma may be used. Those who object to the term leukosarcoma suggest the term sarkoleukemia, but, as Paltauf⁴³ replies, this latter term does not indicate that the invasive process may be primary, as Sternberg and he believe often to be the case.

Ewing⁴⁴ points out that the neoplastic nature of the entire leukemic process has never received general endorsement, but in certain cases the picture varied from the standard type to a true neoplasm. He believes that these differences are best explained by different grades of hyperplasia. Cases of leukosarcoma, such as this one, bear out this idea in a striking way, by bridging the gap between typical leukemia and lymphosarcoma.

Summary and Conclusions.—A white man, aged sixty years, gave a history of a swelling in the right inguinal region for twelve months. A biopsy showed lymphosarcoma. A roentgenogram revealed a tumor in his pelvis. The leukocyte count was normal. He was given Roentgen ray treatments for four to five months, during which time several examinations of the blood were negative. In the following month he developed a leukemia, the white blood count rapidly increasing to 444,000 cells per c.mm. at the time of death and the differential blood count showing 90 to 96 per cent small lymphocytes. The autopsy revealed a primary, invasive lymphosarcoma in the inguinal and retroperitoneal regions, an extensive involvement, resembling leukemia, of most of the lymphoid system, liver, spleen and bone marrow of the right femur, and metastatic nodules in most of the organs. In the tissues there were both large lymphoblasts and small lymphocytes, with intermediate types and in various combinations, indicating that these cells represent different degrees of hyperplasia or differentiation. The picture appears intermediate in character between typical lymphosarcoma and lymphatic leukemia, rather than a combination of two separate entities. The case falls in the group of leukosarcoma.

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CHANGES IN THE EYE IN LEUKEMIA.*

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SINCE Liebreich (1861) published his original communication on 6 cases of leukemic retinitis, a number of other observations have been recorded on the retinal changes in leukemia. Most reports, however, have been based largely on individual cases. Leber has compiled an excellent summary of the changes in the eye in leukemia, and he has thoroughly reviewed the literature on the subject up to the year 1916. With reference to the frequency of such changes, he stated that, in the Tübingen Clinic, Mayer found retinal hemorrhages in 8 of 21 cases of leukemia during a period of sixteen years. Retinal changes are, however, more common in leukemia than this statement would indicate. Moore reviewed the changes in the eye

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in a group of 25 cases of leukemia observed personally. Retinal changes were present in 23 of the 25. He stated that few, if any, patients die of leukemia, whether lymphocytic or myelogenous, acute or chronic, without at some time showing ocular manifestations.

For the present study, complete clinical data including an ophthalmoscopic examination were available on 138 cases of leukemia. The patients were examined in the various sections on internal medicine in The Mayo Clinic and most of them were seen in consultation with specialists in diseases of the blood. The cases were grouped, on the basis of the diagnosis made by these consultants, into the acute and chronic myelogenous types and the acute and chronic lymphatic types. Seventy-nine of the cases were of the myelogenous type, 7 were of the acute and 72 were of the chronic. Fifty-nine of the cases were of the lymphatic type, 10 were of the acute and 49 were of the chronic. Eighty-nine of the entire group (65 per cent) showed retinal changes. Retinal changes were slightly more common in the acute than in the chronic cases and were more common in myelogenous than in lymphatic leukemia. Of the 17 cases of acute leukemia, 12 (70 per cent) showed retinal changes and of the 121 cases of chronic leukemia, 77 (63 per cent) showed retinal changes. Retinal changes were present in 63 (87 per cent) of the cases of chronic myelogenous leukemia; in 14 (29 per cent) of chronic lymphatic leukemia; in 6 (86 per cent) of acute myelogenous leukemia, and in 6 (60 per cent) of acute lymphatic leukemia (Table I).

TABLE I.—POSITIVE AND NEGATIVE FUNDI IN 138 CASES OF LEUKEMIA.

	Number.	Positive.	Negative.
Acute leukemia	17	12	5
Myelogenous	7	6	1
Lymphatic	10	6	4
Chronic leukemia	121	77	44
Myelogenous	72	63	9
Lymphatic	49	14	35
Totals	138	89	49

Ophthalmoscopic Features of Retinal Lesions. Both Leber and Moore divided the retinal changes found in leukemia into three distinct groups or stages (1) engorged veins or, according to Leber, simple inflammatory hyperemia; (2) engorged veins with hemorrhages, and (3) engorged veins with hemorrhages and definite leukemic infiltrations into the retina, true leukemic retinitis. Of Moore's 23 cases, 3 showed engorged veins, 16 engorged veins with hemorrhages, and 4 leukemic retinitis.

In our series of cases, besides those that could be placed in one or the other of the foregoing groups, there were some with hemorrhages without any noticeable engorgement of the veins, and others with retinitis indistinguishable from that of severe primary or secondary anemia. In 1 case, the retinal changes were indeterminate and

could not be classified. The remaining 88 cases arrange themselves, ophthalmoscopically, into five groups:

Engorged Veins. In 27 of 88 cases, the retinal veins were definitely engorged, but hemorrhage was not present. In some of these, the retinal arteries were also dilated.

Engorged Veins with Hemorrhages or Exudates or Both. In 35 of 88 cases, besides definitely engorged veins, various types of hemorrhage or exudate or both were present in the retina. The exudates, however, were of types not definitely recognizable as leukemic infiltrates. In some of these cases, the disks were full and blurred.

Leukemic Retinitis. In 10 cases, definite leukemic or leukocytic infiltration into the retina was present, particularly in the form of white lines sheathing the peripheral portions of the distended veins, but often also in the form of localized nodules with associated hemorrhages. In almost all of these cases, the disks were full and blurred and in some they were measurably swollen.

Retinal Hemorrhages. In 8 cases, hemorrhage was present in the retina; the retinal veins were not definitely engorged.

Retinitis of Anemia. Eight cases presented a type of retinitis which could not be distinguished ophthalmoscopically from that seen in cases of pernicious anemia or in cases of severe anemia, for example, secondary to carcinoma of the stomach or colon. The fundus in these cases showed definite anemia of the disk and of the blood columns in the retinal and choroidal vessels, usually some dilatation of the retinal vessels, both arteries and veins, scattered hemorrhages, and exudate of the superficial cotton-wool type (localized edema of the nerve fiber layer of the retina). The diagnosis of leukemia was established by the blood counts and other clinical features and was not suggested particularly by the retinal picture.

Many authors^{2,4} stress the peculiar color of the fundus in leukemia. Supposedly it is due to the anemia combined with the excessive number of white cells in the circulation. According to one author,² it depends largely on leukemic infiltration of the choroid. As a matter of fact, the characteristic color is by no means always present and is seldom striking. The disks are usually pale and may be blurred, particularly at the margins. In some of the cases of leukemic retinitis, they are measurably swollen. Characteristically, the retinal veins are markedly distended and tortuous. Their caliber may be two to three or even four to five times that of the arteries and they often appear sausage-like. The arteries are, as a rule, of average normal caliber. They may be dilated and tortuous but never to the same degree as the veins. The pallor of the blood in the vessels is often striking. The veins are frequently rose-red and the arteries pale yellow. Grunert observed a distinct flow of blood in the dilated veins in a case of leukemia with choked disks.

Hemorrhages may be present in the retina either with or without other changes in the fundus. They vary greatly in number and

occur in all parts of the fundus. They may be round or irregularly shaped. They vary in color from very pale to deep red and in size from minute to disk size or larger. Infrequently they have a white halo. Hemorrhagic areas with a small distinct yellowish-white center are common. In a number of cases of acute leukemia, all of these areas were of the irregularly rounded type with more or less definite white centers. A large hemorrhage in front of the retina is sometimes seen, especially in the terminal stages of the disease.

The grayish-white patches, or exudates, in the retina, which are always less than a disk diameter in size, are of two varieties: deep nodules composed of leukocytes, and more superficial patches of varicose nerve fibers simulating the so-called cotton-wool exudates commonly seen in the vascular types of retinitis. The deep nodules are the more common and are characteristic of leukemia. They are usually round, sharply circumscribed, often elevated, and are often surrounded by a hemorrhagic margin. Usually, they are from one-sixth to one-third of a disk diameter but they may be two-thirds to three-fourths of a disk diameter. According to Bettmann, white patches may appear and disappear in a period of from twenty-four to forty-eight hours. He was, however, unable to determine to which of the two types the rapidly appearing and disappearing patches belonged. In true leukemic retinitis, the distended veins are often sheathed particularly in their peripheral portions, with white bands of varying widths. In connection with these perivenous infiltrates, large and often elevated masses of leukocytic infiltration into the retina may develop. In association with these masses, particularly at their margins, hemorrhagic areas are usually seen. When perivenous sheathing is present without much infiltration of the neighboring retina the underlying choroid often appears mottled, probably as the result of leukemic infiltration.

Histologic Characteristics of Leukemic Retinal Lesions. Leber has carefully reviewed the histologic studies of Bettmann, Bondi, Deutschmann, Kerschbaumer, Meller, Murakami and Roth in which leukemic retinal changes were observed during life. Hudson also gave an excellent summary of the histology of leukemic lesions of the eye. Parsons discussed the histologic data and the factors involved in their production. According to Leber the veins and capillaries are markedly dilated in the retina and the leukocytes within the vessels are markedly increased in number. In many cases, the lymph sheaths of the larger vessels are widened and filled with leukocytes; in some of the vessels the walls are infiltrated with leukocytes. Hemorrhages are present in the various layers of the retina, and also aggregations of leukocytes often surrounded by a ring of erythrocytes. Patches of gangliform hypertrophy of the nerve fibers may be present. Mild edema of the disk and retina is common. The optic nerve may be infiltrated with leukocytes. The retinal supporting tissue is often increased in amount.

The choroid is thickened due to dilatation of the blood vessels, particularly the veins, and at times by infiltration of the stroma with leukocytes. This diffuse infiltration of the choroid is apparently due to actual proliferation of extravasated immature leukocytes, since it has been found in cases in which the total number of leukocytes in the blood was not increased. It is usually seen in association with lymphoma of the orbit. Hudson considers the orbital lymphoma as the probable primary lesion, while Meller believes that it arises secondarily by extension from the choroid along the sheaths of the posterior ciliary arteries.

The nodular collections of leukocytes and the areas of gangliform hypertrophy of the nerve fibers found on histologic examination are seen ophthalmoscopically as white patches in the retina. It is difficult to differentiate them during life. The characteristic leukemic pallor of the fundus is dependent on the reduction of the hemoglobin and of the erythrocytes, on the relative and actual increase of the leukocytes in the retinal and choroidal vessels, and at times on the infiltration of the choroid with leukocytes. Deutschmann reported several cases showing the characteristic pale red without any infiltration of the stroma of the choroid. On the other hand, Meller reported a case with dense infiltration of the choroid in which the fundus during life had been of normal color, probably because of the deep pigmentation of the retinal pigment epithelium. It seems, therefore, that leukocytic infiltration of the choroid is a minor factor in the production of the characteristic pallor of the fundus.

The mode of production of the hemorrhagic areas and leukocytic infiltrates in the retina has not as yet been satisfactorily determined. Some authors, notably Verderame and Kerschbaumer, believe that they arise as the result of diapedesis of the blood through the poorly nourished walls of the vessels. According to Leber, supported in part by the observations of Murakami, they are always occasioned by direct escape of blood into the retina through actual rupture of the wall of the vessel following occlusion of the lumen by a mass of leukocytes and subsequent infiltration and softening of the wall. The peculiar characteristics of many of the hemorrhages with the large central collection of leukocytes are due, according to Öller and Murakami, to a tendency of the leukocytes to clump themselves together, or, according to Stock, to a separation of the erythrocytes from the leukocytes in the larger hemorrhages by sedimentation, or, according to Murakami and Meller, to actual proliferation of the leukocytes after their escape into the retina. The leukocytic areas of infiltration without hemorrhagic borders are probably, according to Leber and Murakami, ectasias of capillaries and small veins filled with leukocytes, and, as a result of diapedesis, surrounded by a sheath of leukocytes.

Since none of the eyes observed ophthalmoscopically in our

series was available for microscopic study we cannot offer anything original to the histology of retinal changes in leukemia.

Clinical Significance of the Retinal Changes in Leukemia. Little is found in the literature with regard to the factors influencing the occurrences of retinal changes in leukemia or with regard to the clinical significance of these changes with reference to the type, stage, future course or prognosis in leukemia. Leber stated that the occurrence of extensive hemorrhages in the eye indicates a general hemorrhagic disposition and the likelihood of the occurrence of hemorrhages in other parts of the body such as the subcutaneous tissues. Moore believes that the presence of retinal hemorrhages does not imply a more than usually grave prognosis. He stated that it is not rare to see a complete clearing of the fundus during temporary improvement in the patient's condition. He believes that the change in the composition of the blood affects the nutrition of the endothelium of the retinal vessels in such a way as to allow the escape of the fluid and cellular elements of the blood. Leber stated that the marked dilatation of the retinal vessels may be due to stasis induced by slowing of the blood stream. He does not believe that the type of leukocyte predominating is of any importance in the origin of the retinal changes. He believes that all the pathologic changes in the retina are due to the increase in leukocytes and to the circulatory disturbances produced by the changed composition of the blood. Andrewes and Rolleston suggested that a low platelet count may be a factor in causing retinal hemorrhages in acute lymphatic leukemia.

In view of the paucity of available data, we endeavored to determine the factors involved in the production of the retinal lesions, the stage and type of the disease in which they are most likely to occur, and their significance, particularly with reference to prognosis. If all the varieties of retinal lesions present in the different types of leukemia are considered in one group, it is immediately apparent that no one element of the changes in the blood can be held responsible for the retinal lesions, for changes in the fundus may be present when the leukocytes number as low as 4300, the erythrocytes are as numerous as 4,970,000 and the hemoglobin percentage as high as 75 (Dare). It is of interest also that the eye-grounds may be normal when the leukocytes number as high as 532,000, the erythrocytes as low as 1,440,000 and the hemoglobin percentage is as low as 18 (Dare). With this in view, and in order to make a more critical analysis of the available data, an attempt was made to consider separately each of the five types of retinal lesions in each of the four types of leukemia.

Retinitis of anemia occurred most frequently in acute myelogenous leukemia. The other types of retinal changes were present most often in chronic myelogenous leukemia. Engorged veins alone and engorged veins with hemorrhage and exudate were found

in all types of leukemia. Hemorrhage alone, without engorged veins, was found in all types with the exception of acute myelogenous leukemia. Characteristic changes in hemoglobin percentage, total erythrocytes or total leukocytes were not found to persist throughout the group of cases, showing engorged veins with or without hemorrhages and exudates or hemorrhages alone. The engorgement of the veins is sometimes due to the increased number of leukocytes. At other times, it is apparently a part of the dilatation of the vessels which usually occurs in severe anemia either as the result of lowered nutrition of the walls of the vessels or of lowered blood pressure. Hemorrhage into the retina either alone or in association with dilated veins is often the result of anemia and the resultant poor nutrition of the walls of the vessels. Sometimes the hemorrhage seems to occur as a part of a general hemorrhagic tendency. In these cases and also in others in which, near the terminal stage of the disease, they assume a purpuric form, the hemorrhages are often associated with a lowered platelet count. A definite relationship cannot, however, be established in general between the platelet count and the occurrence of retinal hemorrhages (Table II). The combination of engorged veins with hemorrhages

TABLE II.—RELATION OF PLATELET COUNT TO RETINAL HEMORRHAGES.

Type of leukemia.	Without hemorrhages.	With hemorrhages.
Acute lymphatic . . .	20,000 to 54,000 (2 cases)	20,000 to 280,000 (2 cases)
Acute myelogenous	68,000 to 320,000 (2 cases)
Chronic lymphatic . . .	60,000 to 310,000 (3 below 100,000) (6 above 100,000)	54,000 to 280,000 (1 below 100,000) (2 above 100,000)
Chronic myelogenous . . .	88,000 to 780,000 (1 below 100,000) (13 above 100,000)	84,000 to 1,022,000 (3 below 100,000) (11 above 100,000)

and exudates is the most common retinal change in leukemia. The blood picture in cases presenting this type of retinitis is by no means uniform. In some cases the retinitis is probably due to the associated anemia. It is well known that anemia can cause the superficial type of cotton-wool exudate which is represented histologically by localized varicose hypertrophy of the nerve fibers. For the production of the nodular exudates typical of leukemia, however, actual leukocytic infiltration of the retina is necessary. As the total leukocyte count is not increased in some of these cases, the infiltration must depend on the invasive powers of the immature leukocytes rather than on the actual increase in their number.

Leukemic retinitis in its restricted sense with the characteristic leukemic infiltration into the retina, particularly along the veins, was found only in cases of chronic myelogenous leukemia. It was present in 10 of the 72 cases of this type. The infiltration was never

present except with a high total leukocyte count, the lowest count in the 10 cases being 45,300 and the highest 588,000. In all the cases of leukemic retinitis, the percentage of myelocytes and myeloblasts in the differential count was quite high. The percentage ranged from 16 to 60 and was below 30 in only 1 of the 10 cases (Table III).

TABLE III.—ACUTE MYELOGENOUS LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNTS.

	Negative (1 case).	Engorged veins (1 case).	Engorged veins with hemorrhage and exudate (1 case).	Retinitis of anemia (4 cases).
Range of leukocytes	8,100	4,800 to 8,400	5,100	6,600 to 46,200
Range of erythrocytes	2,970,000	2,920,000 to 2,520,000	1,450,000	950,000 to 2,060,000
Range of hemoglobin, per cent . . .	55	45 to 60	28	15 to 35
Range of polymorphonuclears, per cent	16	50	13	10 to 32
Range of lymphocytes and lympho- blasts, per cent	15	45	24	15 to 39
Range of myelocytes and myeloblasts, per cent	65	..	53	19 to 73*

* 3 above 30; 1 below 30.

In the 8 cases of leukemia presenting the ophthalmoscopic picture of retinitis of anemia, the changes in the blood were always those of secondary anemia of a rather severe grade. In these cases, the hemoglobin ranged from 15 to 40 per cent (Dare) and the erythrocytes from 950,000 to 2,600,000. This type of retinitis occurred in all the types of leukemia except the acute lymphatic type.

It is evident, then, that the type of retinal lesion found in cases of leukemia depends, to some extent at least, on variations in the blood picture. It is of interest also to consider separately each of the varieties of leukemia and to note in each the factors concerned with the onset of hemorrhagic and exudative lesions in the retina.

According to Vogel, and Ordway and Gorham, both varieties of acute leukemia present essentially the same clinical picture and run the same course. From the standpoint of retinal changes, they can be considered together. In the acute types of both lymphatic and myelogenous leukemia, the essential cause of the appearance of retinal lesions seems to be anemia. In these cases, as in pernicious anemia, it is rare to find retinitis when the hemoglobin is above 40 per cent (Dare) (Tables III and IV). That the tendency of the immature leukocytes to infiltrate the walls of the vessels and the tissues is also a factor in the production of the retinal lesions is

shown by the frequency of hemorrhagic areas with definite nodular white centers. A lowered platelet count may also be concerned in the causation of hemorrhages. In our series, however, hemorrhages were not always present when the platelet count was lowered.

TABLE IV.—ACUTE LYMPHATIC LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNT.

	Negative (4 cases).	Engorged veins (2 cases).	Engorged veins with hemorrhage and exudate (3 cases).	Hemorrhage only (1 case).
Range of leukocytes	7,300 to 360,000	12,000 to 1,653,000	4,300 to 76,000	98,000 to 139,000
Range of erythrocytes	1,740,000 to 4,740,000	2,010,000 to 3,340,000	900,000 to 2,250,000	1,760,000 to 2,220,000
Range of hemoglobin, per cent . .	18 to 65	21 to 44	15 to 45	21 to 40
Range of polymorphonuclears, per cent	1 to 7	1.3 to 47.5	0.5 to 7	
Range of lymphocytes and lympho- blasts, per cent	90 to 97.5	47.5 to 98.7	88 to 99.5	99

In chronic myelogenous leukemia, the hemoglobin ranges definitely lower and the percentage of myelocytes in the differential count is definitely higher in the cases with retinal lesions than in those without them. It would appear that, except in retinitis of the anemic type, a high percentage of myelocytes and myeloblasts is the most essential feature for the production of retinitis, being much more significant than a high total leukocyte count (Table V).

In chronic lymphatic leukemia, the factors influencing the onset of retinal lesions seem rather less definite than in the other types. The most significant cause would seem to be the associated anemia. The percentage of lymphoblasts and lymphocytes in the differential count is more uniformly high in the cases with retinal lesions than in those without them, particularly in cases showing exudates in the retina. Since, however, definite infiltration into the retina along the veins was not noted in any of the cases, the relatively high percentage of lymphocytes must be of secondary importance in the production of retinitis. Some of the retinal exudates are probably lymphocytic infiltrations, but the tendency of the cells to invade the retina seems to be definitely less in lymphatic than in myelogenous leukemia (Table VI).

As previously reported by Wagener, ophthalmoscopic examination showed typical lipemic retinitis in a case of acute lymphatic leukemia. On analysis, the blood was found to contain 5 per cent total fats. The lipemia, which had developed coincident with a rather rapid fall in the hemoglobin percentage to 31 and of erythro-

TABLE V.—CHRONIC MYELOGENOUS LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNTS.

	Leukemic retinitis (10 cases).	Negative (9 cases).	Engorged veins (20 cases).	Engorged veins with hemorrhage and exudate (26 cases).	Hemorrhage only (5 cases).	Retinitis of anemia (2 cases).
Range of leukocytes	45,300 to 588,000	19,200 to 378,000	12,900 to 545,000	9,500 to 575,000	149,000 to 317,000	17,300 to 32,500
Range of erythrocytes	2,120,000 to 3,910,000	3,330,000 to 4,680,000	1,500,000 to 4,810,000	1,850,000 to 4,460,000	2,550,000 to 3,890,000	2,090,000 to 2,220,000
Range of hemoglobin, per cent	30 to 60	53 to 78	28 to 69	23 to 75	42 to 60	37 to 40
Range of polymorphonuclears, per cent	30 to 56	48 to 70	6 to 70	13 to 65	30 to 64	42 (only 1 differential)
Range of lymphocytes and lymphoblasts, per cent	1 to 4.5 16 to 60 (only 1 below 30)	0.5 to 15 8 to 42 (only 1 above 30)	0.5 to 85 6.5 to 45 (13 above 30) (7 below 30)	0 to 47 0 to 70 (15 above 30) (8 below 30)	1 to 7 32 to 45 (4 above 30) (none below 30)	5 23
Range of myelocytes and myeloblasts, per cent						

TABLE VI.—CHRONIC LYMPHATIC LEUKEMIA: TOTAL AND DIFFERENTIAL BLOOD COUNTS.

	Negative (35 cases).	Engorged veins (4 cases).	Engorged veins with hemorrhage and exudate (5 cases).	Hemorrhage only (2 cases).	Retinitis of anemia (2 cases).
Range of leukocytes	3,000 to 532,000	31,400 to 334,000	248,000 to 957,000	41,700 to 51,200	7,500 to 238,000
Range of erythrocytes	1,440,000 to 5,160,000	2,780,000 to 4,480,000	980,000 to 4,050,000	1,670,000 to 3,760,000	1,540,000 to 2,000,000
Range of hemoglobin, per cent	20 to 91	50 to 76	12 to 67	25 to 60	15 to 30
Range of polymorphonuclears, per cent	1 to 33	1 to 14	0 to 3.5	5.5 to 16	4 to 12
Range of lymphocytes and lymphoblasts, per cent	64 to 99 (20 below 90) (15 above 90)	79 to 98 (2 below 90) (2 above 90)	91 to 99 (all above 90)	77 to 93 (1 above 90) (1 below 90)	85 to 93 (1 below 90) (1 above 90)
Range of myelocytes and myeloblasts, per cent	0	0	0	0	0

cytes to 1,000,000, disappeared with improvement in the blood picture following transfusion, the hemoglobin rising to 55 per cent and the erythrocytes to 3,340,000.

In lymphatic leukemia, the occurrence of retinal hemorrhages may be taken as indicative of a tendency to the occurrence of hemorrhages in other tissue; such as, the skin, subcutaneous tissues, and mucous membranes. In myelogenous leukemia, retinal hemorrhages do not seem to have the same significance with regard to hemorrhages elsewhere. Apparently, in myelogenous leukemia, hemorrhages occur in the retina much more frequently than in other tissues, while in lymphatic leukemia, the reverse is true. In acute myelogenous leukemia, petechiæ were present in the retina in 4 cases and in other tissues in 3. In chronic myelogenous leukemia, petechiæ were present in the retina in 45 cases and in other tissues in 9. In 4 other cases there was a history of hemorrhage in other parts of the body. In acute lymphatic leukemia petechiæ were present in the retina in 4 cases and in other tissues in 7. In chronic lymphatic leukemia, petechiæ were present in the retina in 9 cases and in other tissues in 10, and in 9 other cases there was a history of hemorrhage in other parts of the body.

There does not seem to be any definite stage of leukemia at which we can expect to find retinal lesions. Retinitis has been seen as early as three weeks after the onset of symptoms, and in the chronic cases normal fundi have been found as late as ten years after the onset of the disease.

In this series, the cases were not traced carefully over a sufficiently long period to make possible an exact determination of the prognostic value of the retinal changes in estimating the probable length of life of the patients. In the acute cases, the presence or absence of retinitis does not seem to furnish any index as to the length of life. It is of interest, however, that a marked increase in the size and number of hemorrhages into the retina was observed a few days before death in several cases of an acute or subacute form of the disease. In the chronic cases, retinal changes appear to be of some prognostic value. In chronic lymphatic leukemia, the average length of life after observation was two hundred and forty-eight days for the patients without retinitis and seventy-two days for the patients with retinitis. In chronic myelogenous leukemia the average length of life was ten hundred and thirty-nine days for the patients without retinitis and three hundred and fourteen days for the patients with retinitis (Table VII).

The effect of radium treatment of the leukemia on retinitis was carefully observed in only 1 case. This patient, a boy, aged eight years, entered the hospital June 24, 1926, with symptoms of three weeks' duration. A diagnosis of chronic myelogenous leukemia was made. On admission, the spleen was very large, extending below the level of the umbilicus; the hemoglobin was 30 per cent

(Dare), the erythrocytes numbered 2,550,000 and the leukocytes 588,000 of which 49 per cent were myelocytes and leukoblasts. At intervals of about seven days, radium was applied to the splenic area, a total of 19,400 mg. hours being given. His general condition improved considerably. At the end of the period of treatment, the spleen was only about a fourth of its original size, the hemoglobin was 45 per cent (Dare), the erythrocytes numbered 3,330,000, and the leukocytes 72,000, 34.5 per cent of which were myelocytes and leukoblasts. Before radium treatment was begun, ophthalmoscopic examination showed typical leukemic retinitis characterized by distinct edema of the disk and retina, tremendous engorgement of the veins and some dilatation of the arteries with a very pale, almost lipemic, appearance of the blood, numerous hemorrhagic and exudative areas in the retina, and definite leukocytic infiltration around the veins. Following treatment, the edema of the disk and retina almost disappeared, the dilatation of the veins was much less marked, the perivenous leukocytic infiltration was much less definite, and the number of hemorrhagic and exudative areas in the retina was considerably diminished.

TABLE VII.—COMPARISON OF LENGTH OF LIFE IN CASES WITH AND WITHOUT RETINITIS.

Type of leukemia.	Shortest life, days.		Longest life, days.		Average life, days.	
	With retinitis.	Without retinitis.	With retinitis.	Without retinitis.	With retinitis.	Without retinitis.
Acute myelogenous	4	34	64	34	35	34
Acute lymphatic	131	8	131	21	131	14
Chronic myelogenous	30	1039	1080	1039	314	1039
Chronic lymphatic	2	51	310	523	72	248

External Ocular and Orbital Changes.—External changes in the eye were infrequent in this group of leukemic cases. In 1 case of chronic myelogenous leukemia, slight ptosis of the upper lid was seen, in 2 cases slight inequality of the palpebral fissures, and in 1 case subconjunctival hemorrhage. In chronic lymphatic leukemia, edema of the lids was noted in 3 cases, subconjunctival hemorrhages in 4, and ecchymosis of the lids in 1. Ecchymosis of the lids was seen in 1 case of acute lymphatic leukemia. In 1 case of chronic lymphatic leukemia, at the time of the first examination the palpebral fissures were of unequal width and the accessory lacrimal glands were somewhat hypertrophied. A few months later, proptosis of the left eye developed probably due to lymphoma of the orbit.

Changes in the size and shape of the pupils and in their response to light and convergence seldom occur as the result of leukemia. When they do occur, they, like the narrowing of the palpebral

fissure and apparent ptosis previously noted, are probably due to pressure on the sympathetic nerves by enlarged cervical nodes. In one of our cases of chronic myelogenous leukemia, one pupil did not react to stimulation by light and contracted only slightly in convergence. A cause, aside from the leukemia, could not be found to account for the sluggish reflexes.

A history of blurred vision was given in only 8 of the cases of the series. Marked loss of vision was noted in only 2 cases. In one of these, vision was reduced to the ability to count fingers at half a meter and to six-thirtieths in the right and left eyes respectively, as the result of hemorrhage and exudates at the macula. In 1 case there was paracentral scotoma of one eye, due to a large hemorrhage near the macula. Gross defects in the peripheral fields of vision were not noted in the series.

Summary and Conclusions. In 138 cases of leukemia, retinal lesions were found in 70 per cent of the acute cases and in 63 per cent of the chronic cases, in 87 per cent of the myelogenous type and in 34 per cent of the lymphatic type.

The most common retinal picture in leukemia is that of engorged veins associated with hemorrhagic areas and with exudates of deep nodular or superficial cotton-wool type. It is found in acute and chronic cases of both lymphatic and myelogenous types.

The typical hemorrhagic area of acute leukemia is irregularly rounded with a nodular white center. When this type of hemorrhage occurs exclusively, or almost so, the diagnosis of acute leukemia is usually justified. Similar hemorrhages are found in association with the other retinal lesions in chronic leukemia.

Leukemic retinitis, showing, besides other lesions, definite leukocytic infiltration into the retina and choroid along the line of the retinal veins, was found in this series only in cases of chronic myelogenous leukemia. In all cases it was associated with a high leukocyte count and with a relatively high percentage of immature leukocytes in the blood.

In acute leukemia, the retinal lesions are due mainly to the anemia.

In chronic myelogenous leukemia, the main factors in the cause of retinal lesions are anemia and the high percentage in the blood of immature leukocytes of the myeloblastic type.

In chronic lymphatic leukemia, the main factor in causing the retinal lesions is the associated anemia. A high percentage of immature lymphocytes may be a factor in certain cases.

In myelogenous leukemia, hemorrhage in the retina is more common than in the skin, subcutaneous tissues, and mucous membranes. In lymphatic leukemia the reverse is true.

Retinal lesions may be seen in leukemia as early as three weeks after the onset of symptoms, and a normal fundus may be found as late as ten years after the initial symptoms of the disease.

In chronic leukemia the average subsequent length of life was

considerably less in cases with retinal lesions than in those with a normal fundus at the time of the first examination.

In one case of chronic leukemia marked improvement in the retinal lesions and considerable improvement in the general physical condition followed radium treatment.

Infiltration of the lids and orbit and subconjunctival ecchymosis and ecchymosis of the lids are relatively infrequent in leukemia.

Pupillary and visual field changes as a result of leukemia are rare.

Definite reduction of vision was present in only 8 per cent of the cases of leukemia.

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ON THE GENERALIZED EFFECT OF RADIATIONS IN MYELOGENOUS LEUKEMIA.

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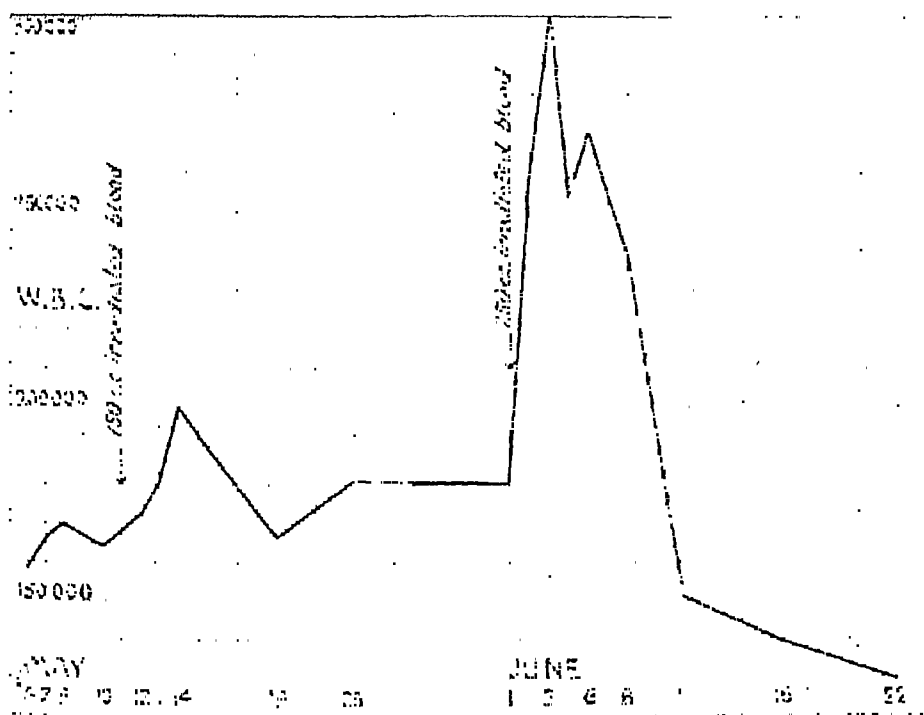
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IN a previous paper¹ on the effect of radium applications on the morphology of the blood in myelogenous leukemia, the following conclusion was reached: "The mechanism of action of radium upon the leukemic foci is of a generalized as well as localized nature." In other words, when radium is applied to any portion of the body, its effect is carried by the blood stream to the leukopoietic foci. Thus, from a local application, a generalized action is obtained. The purpose of the present paper is to present definite evidence in

support of this view, using the clinical material of 2 cases of myelogenous leukemia, treated with the rays.

Case Reports. CASE I.—Mrs. E. W., aged thirty-two years, housewife, was admitted to the Misericordia Hospital on May 4, 1927. The patient stated that about a year before admission she first had a sensation of weight on the left upper side of the abdomen. Later she was able to palpate there a mass, which grew steadily in size. The patient did not lose weight, and had no serious disturbance except for slight loss of strength.

Upon admission, the patient appeared pale but in fair condition of nourishment. The left side of the abdomen was bulging and on palpation a hard mass was found which reached from the costal margin down the crest of the iliac bone. The lateral limits of the mass were the left lateral sternal line and the left anterior axillary line. The urine contained a cloud of



CASE I.—Effect of autotransfusion of irradiated blood on the leukocyte count in a case of myelogenous leukemia.

albumin. The blood urea was 13 mg.; creatinin, 1.8 mg.; uric acid, 3.4 mg., per cent. The basal metabolic rate was + 32 (Harris and Benedict standard). The blood-coagulation time was four and a half minutes, the bleeding time fifteen minutes. The hemoglobin content was 12.8 gm. per cent; the erythrocytes were 3,230,000; the leukocytes 158,400. The differential count was: hemocytoblasts, 6.5 per cent; myeloblasts, 3 per cent; promyelocytes, 11.5 per cent; myelocytes, 13 per cent; metamyelocytes, 9 per cent; neutrophilic polymorphonuclears, 44.5 per cent; eosinophils, 4 per cent; mast cells, 6 per cent; lymphocytes, 2.5 per cent; normoblasts, 2 per cent.

The diagnosis of myelogenous leukemia was made. For a week from the day of admission, daily complete blood counts were made to determine the fluctuation of the number of cells. The patient did not receive, during the period of observation, any drug or therapeutic treatment, except those here reported.

The average number of leukocytes per cu.mm. for the week ending May 11, was 165,320, and the maximum variations were within 4.4 per cent.

On the morning of May 11, 150 cc. of blood were removed by venesection, mixed with sodium citrate solution in a sterile Pyrex beaker, covered with a thin layer of gauze. This was immediately irradiated, with 10 per cent of an erythema dose of filtered rays.

Within ten minutes from the time of removal, the blood was reinjected into the patient. There was no reaction following this procedure, except a very slight chill in the afternoon. Twenty-four hours later, the leukocytes were 172,000; two days later, 181,000; three days later, 200,000. In eight days they were back within the limits established before. The temperature fluctuated from 98° to 100° F. with daily elevations; the pulse from 76 to 110; respirations were 24.

Uric acid rose to 8.2 on May 20. Oozing of blood occurred from the venesection wound, and lasted until May 21. The coagulation time was four minutes, but the bleeding time was a little over fifteen minutes. The platelets were 300,000 per cu.mm.

On May 23, a perceptible diminution in the size of the spleen was noticed.

On May 30, the lower border of the spleen was 4 cm. above the umbilical line and the patient felt well. The leukocyte count for the last week of May had averaged 180,500, with variations well within 2 per cent.

On June 1, 250 cc. of blood were removed from the patient, mixed with sodium citrate solution and irradiated, with 20 per cent of an erythema dose of filtered rays, and reinjected into the patient within fifteen minutes from the time of removal.

The patient had no reaction following the autotransfusion. Twenty-four hours after the injection of irradiated blood the leukocytes were 258,000; two days later 300,000. Free bleeding occurred from the phlebotomy wound during the week following the autotransfusions; on the night of June 3, the patient lost about 500 cc. of blood. The coagulation time was five minutes, but the bleeding time was extended over one hour.

On June 4, the uric acid in the blood was 12 mg. per cent. Slight oozing of blood continued up to June 6.

The number of leukocytes slowly diminished and on June 22, without any further treatment, they were down to 130,000 or 22 per cent less than the average before the treatment was started. The lower border of the spleen on the same date was about 4 cm. above the umbilicus.

The changes in the differential count may be summarized as follows: The primordial cells before the treatment were 6.5 per cent and the immature cells of the granulocytic series 33 per cent. Forty-eight hours after the first autotransfusion of radiated blood, the primordial cells rose to 9 per cent and the immature cells of the granulocytic series to 41 per cent. There was also a distinct increase in the number of lymphocytes, and megakaryoblasts, previously absent, made their appearance in the circulating blood. Similar changes occurred after the second autotransfusion.

Summary of Case I. A young white woman, with an early untreated myelogenous leukemia received two autotransfusions of irradiated blood. After each one of the transfusions, blood changes occurred, in all respects similar to those obtained where radiations are applied to the body (long bones). A marked diminution of the spleen was also obtained.

CASE II.—J. M., an adult Negro, aged forty-five years, laborer, was admitted to the Philadelphia General Hospital, September 1, 1925. The patient had had smallpox, typhoid fever, malaria, syphilis and gonorrhea. About sixteen months before admission, he first complained of weakness accompanied by rise of temperature. Three months before admission, the

patient noticed an enlargement of the abdomen and swelling of the legs. On admission, there were signs of fluid in both thoracic cavities below the fourth rib; a double murmur could be heard over the aortic area of the heart; there was moderate ascites, enlarged liver, and enlarged spleen. The latter reached down below the crest of the iliac bone, and to the right the umbilical line. The lower extremities and scrotum were edematous. Dyspnea was present throughout his short stay in the hospital. The temperature varied from 96° to 100° F., the pulse from 80 to 100, and respiration from 20 to 30.

The blood examination, done on admission gave the following result: hemoglobin, 47 per cent; erythrocytes, 2,507,000; leukocytes, 153,000. The differential count showed 57 per cent of immature granulocytic cells, and 35 per cent of neutrophilic polymorphonuclears. A diagnosis of myelogenous leukemia and syphilitic aortitis, with regurgitation, was made.

A paracentesis was performed; the puncture wound oozed a small amount of blood up to the end. A first radium application was given on September 4 over the sole of the left foot, the left internal malleolus, and the lower third of the left leg. On September 5, the leukocytes rose to 291,000 at 9 A.M. That afternoon at 2 o'clock, they were 298,000.

The following day, another radium application was given, over the sole of the right foot, the right internal malleolus, and the lower third of the right leg. On September 6, at 10 A.M. the leukocytes were 103,000. The patient died at 2.30 P.M. the same day from rapidly progressive cardiac decompensation.

The changes in the differential counts can be briefly summarized as a marked increase in the number of the primordial cells (from 14 per cent to 28 per cent) and the appearance of megaloblastic cells. Such changes have been previously found to be a feature of first radium application.¹

Autopsy was performed twenty-four hours after death. Myeloid infiltration of all organs was the outstanding feature. The spleen weighed 3400 gm. and liver 4850 gm. There was a typical syphilitic aortitis with retraction of the valvular leaflets, and the liver showed gummas.

Particular attention was paid to the bone marrow, with the following results: the bone marrow of both tibiae, upper and lower portions, was yellow, fatty and contained spongy bone. It appeared altogether as nonfunctioning adult bone marrow. The marrow of the bones of both feet was identical in structure and appearance with the bone marrow of the tibia. The bone marrow of the femur and of the sternum was red and gelatinous with few hemorrhagic points. From all of these portions of the bone marrow, smears were made, also paraffin sections that were stained with May-Gruenwald-Giemsa, according to Pappenheim's method, and frozen sections, which were stained with the oxidase stain.² The results of the examinations were as follows:

Upper tibia (nonradiated)
Lower tibia (radiated)
The bones of the foot (radiated)

Numerous bony spicules are scattered throughout the fatty marrow with few cells grouped in small foci; no fibrosis; no degenerative changes. The few cells found resemble those of the bone marrow of the femur; the differential count being comparable with that obtained on smears from the femur; about 70 per cent of cells contain oxidase granules.

Femur (sections from several portions)
Sternum

Numerous granulocytic cells, mature, immature, and pathological. Numerous immature and embryonic cells of the erythroblastic series. Seventy per cent of the cells contain oxidase granules.

Aplastic bone marrow in the tibia accompanied by hyperplastic changes in other bones has been observed by the author in a long series of cases including all forms of anemia, acute and chronic leukemia, and acute and chronic inflammatory processes, especially sepsis, accompanied by profound changes of the blood picture. It appears therefore, that the bone marrow of the tibia is a poor index of the general conditions of the bone marrow. Since the bone marrow of the tibia is readily accessible, it has been often depended upon at autopsies to indicate the general condition of the bone-marrow; a practice which should be discontinued.

Summary of Case II. An adult Negro with advanced myelogenous leukemia was given two radium treatments on consecutive days, the emanation tubes being applied over the lower third of both tibiae and the short bones of both feet. That the application had effect was evidenced by the sudden rise in the number of leukocytes, followed later by a sharp drop, and by the conspicuous changes in the differential blood count. At autopsy, it was found that there was no hyperplastic bone marrow in either tibia, nor in the short bones of the feet, but only fatty aplastic bone marrow; also that there was no difference whatever, between the bone marrow of the bones which had been radiated, and of some that had not been radiated. This was especially evident, comparing smears and sections of the lower third of the tibia, radiated, and the upper third of the tibia, which had not been radiated.

Discussion. In the first of the cases presented, it is obvious that the radiations as such or their effects were carried by the whole blood irradiated.

In the second, it would be very difficult to trace a direct effect of the radium applications upon the bone marrow of the bones irradiated. The effect of the radium emanations upon the hemoplastic foci must be explained on the ground that the radium emanations as such are carried by the blood or that they act through the production of leukotoxins, which are produced by the direct effect of the radium emanations upon the white cells of the blood in superficial vessels, or perhaps upon fixed cells of the reticuloendothelial system.

In fact, in the second case, there was *no active* bone marrow in the bones radiated, and there was no difference between the portions irradiated, and those *not* irradiated.

The literature¹ on the subject of the application and possible mechanism of action of radiations in chronic myelogenous leukemia, shows a great disparity of views among workers as to the best place to apply radiations in treating myelogenous leukemia. This observation, and the fact that regardless of the place of application very similar results are obtained, lends support to the view that the direct action of radiations upon the hemopoietic foci is altogether unimportant. In all cases the blood acts as carrier of radiations, either as such or modified, to the hemopoietic foci, where its main action takes place. A very interesting observation was made by Kotzareff

and Weyl:³ they found that the intravenous injection of auto-serum charged with emanations results in the fixation of the emanations by embryonic or neoplastic cells. We have not been able to find whether or not such observations have been confirmed. Should they be, aside from their practical importance in the diagnosis and treatment of malignant growth, they would greatly aid in settling the question of the mechanism of action of radiations on leukemia. At present, experimental work on animals is being carried on to throw new light on the question.

Conclusions. Radium and Roentgen ray affect the hemopoietic centers by an indirect generalized action rather than by a direct local effect. It is not yet clear whether this indirect effect is produced by the blood transfer of emanations to the bone marrow, or by the extramedullary production of leukotoxins, which are then transported to the bone marrow.

In the treatment of myelogenous leukemia by radium or Roentgen ray it is the dosage rather than the place of application that is important.

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INFECTION AS A CAUSE OF JUVENILE CIRRHOSIS.*

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CIRRHOSIS has no definite age period of occurrence; cases occurring in infants are not rare. Mackay¹¹ reports a case beginning in a babe aged eleven days and ending fatally twenty-seven days later. Abt² records a case beginning at two weeks of age and progressing to a fatal termination five months later. Postmortem examination confirmed the diagnosis in each case. It appears that cirrhosis in the newborn is rare, and that the frequency of occurrence increases with age. Seitz¹⁴ summarizing 320 cases, found 31 among sucklings, 72 in young children and 217 in children of school age. Among these were occasional instances in which several children in the same family died of cirrhosis.

* The experimental work reported here was made possible through funds from the Martin Research Foundation.

Cirrhosis occurring in the young presents certain important differences from that seen in adults. Marked enlargement of the spleen is an early and almost constant feature. I have collected data from several hundred reported cases: marked splenic enlargement has been an associated feature in more than 90 per cent. The spleen is often of huge dimensions approximating those found in leukemia. Concurrent with the enlargement of spleen and liver, anemia of gradual onset is usual. Cirrhosis in children occurs in the same general forms as in adults, but cirrhosis of the biliary type occurs more frequently than in adults. The occurrence of intermediate or mixed forms is very frequent. This discussion will be limited to those forms, often designated as hypertrophic and atrophic, which are analogous to the portal cirrhosis of adults. It is understood that the term hypertrophic is often assigned because of the increased size of the liver. Such increase in size is a regular feature of the early stages of the process which ends in the typical "hob-nailed liver" of atrophic or portal cirrhosis. This form of enlarged liver occurs very frequently in children, and the designation hypertrophic cirrhosis does not necessarily imply a different form of disease. Cirrhosis in children is more acute and runs a more rapid course than in adults.

Many pathologists¹⁷ discuss cirrhosis as chronic hepatitis. This conception contributes to a clearer understanding of the process, since hepatitis implies inflammation-reaction to injury which may be the result of diverse causes. Hepatitis properly includes the cellular degeneration and fatty changes, resulting in increased size of the organ—hypertrophy—in the early stages. It includes the cellular destruction, and the resulting active proliferation of both liver cells and bile ducts. It includes the infiltration with inflammatory cells, and the reparative proliferation of fibrous tissue, the contraction of which results in the decreased size—atrophy—of the later stages.

The assembled evidence indicates that juvenile and adult cirrhosis do not differ in etiology. In case reports of juvenile cirrhosis the causative agents most frequently assigned are alcohol, vaguely defined intoxications, congenital anomalies and infections.

If alcohol were the chief primary cause, the condition should occur in a much higher percentage among those addicted to its use than among nonusers. A drug capable of producing such change should have a demonstrable toxicologic action, as do mercuric chlorid, phosphorus, chloroform, or other drugs whose effects can be shown readily by experiments on animals. Cirrhosis has not followed the use of alcohol experimentally. This fact, together with the frequent occurrence of cirrhosis in those having no alcoholic history and its relative infrequent occurrence in alcoholic habitues, indicates the importance of other factors than alcohol. Adami³ commented on the failure of alcohol to produce characteristic cirrhosis in animals

and stated that "extreme cirrhosis may attack children and adults who have never taken a particle of alcohol either medicinally or otherwise." Excessive use of alcohol produces fatty infiltration of the liver in man and in animals. In this connection, the experiments of Opie¹⁵ are significant. He was able to produce cirrhosis in animals by first causing degeneration of the liver by the administration of chloroform, then inoculating living bacteria intravenously. Streptococci were used in some of his experiments; in others *Bacillus coli* was used. He believed the chloroform acted to lower the resistance of the liver rendering it subject to the infection. He suggested the possibility that alcohol may play a rôle similar to that of chloroform in these experiments. The combined action of two factors, as lowered local resistance resulting from injury by alcohol, chloroform or other agents, plus bacterial infection, has received less attention than it seems to merit.

Space does not permit a review of the evidence on toxic cirrhosis. Its importance is generally recognized and has been substantiated by experiments on animals. A number of injurious substances, quite diverse in character, have been used to produce cirrhosis more or less closely resembling that occurring in man.

That congenital abnormalities may occasionally be of such kind as to result in cirrhosis is admitted. There is evidence that this cause is frequently assigned when cirrhosis of unknown origin would be a proper diagnosis. Cirrhosis due to congenital abnormalities is seldom verified by postmortem examination.

Infection is frequently mentioned among etiologic factors. In his summary of 320 cases, Seitz stated that about 33 per cent were of infectious origin. Supporting this view is the frequent occurrence of fever, malaise, nausea, rapid pulse and other evidences of infection. Leukocytosis is present in a considerable proportion of cases. When the leukocytes are not increased, a leukopenia is usually present. The splenic enlargement and anemia which mark the early stages of cirrhosis could be produced by a chronic infection as readily as by toxic agents. The histologic alterations present resemble those of a chronic infection. The leukocytic infiltration, and the active reparative processes seen in rapidly developing cirrhosis are typically the reaction called forth by chronic infection. Syphilis, kala azar and other tropical infections may produce cirrhotic changes indistinguishable from the type under discussion. The demonstration of the parasites in the liver substance in these diseases is accepted as evidence of the causative agent. That other infections than those mentioned may produce a similar result is probable.

Bingel⁵ made examinations of the livers in fatal cases of scarlet fever. In each case he noted extreme degeneration and necrosis of the liver cells and inflammatory infiltration about the vessels. In the liver of a case in which death followed a protracted attack

of scarlet fever he found those same changes present, but in addition there was the rapidly proliferating fibrous tissue which characterizes early cirrhosis. He regarded the fibrous proliferation as an attempt to repair the injury resulting from the infection. Several writers comment on the occurrence of cirrhosis following scarlet fever and measles.

In a case reported by Mya,¹³ cirrhosis developed during the course of a prolonged enteritis. At postmortem examination chronic ulceration enteritis was found, and cirrhosis of atrophic type. Others comment on the development of cirrhosis during the course of chronic infections such as bronchitis, pleuritis, meningitis, arthritis and endocarditis. Edwards⁷ in a review of 100 cases found an active associated infection in 25 per cent of them.

Bolton⁶ reported a case of cirrhosis in a child in which the postmortem examination showed a purulent peritonitis without apparent cause. He believed the cirrhosis was produced by infection of the liver, which finally spread to the peritoneal surfaces. In cases of cirrhosis an associated pleuritis, pericarditis or peritonitis is often found at postmortem and the occurrence of inflammatory adhesions about the liver and spleen is particularly frequent. These suggest infection rather than intoxication with chemical or metabolic products.

Levi,¹⁰ in 1898, reported a case in which cirrhosis was concurrent with mitral endocarditis in a boy, aged seventeen years. He cultivated from the liver a diplococcus which was pathogenic to guinea pigs.

Adami³ investigated an epidemic disease of cattle of which cirrhosis, resembling that occurring in man, was the prominent pathologic feature. He found minute coccoid bacilli in the livers in great numbers. When cultivated, this organism resembled somewhat the bacillus of hemorrhagic septicemia. When injected into rabbits the infection localized in the liver, producing degeneration and necrosis of liver cells. The rabbits died before cirrhotic changes had time to develop. Having established the infectious nature of cirrhosis in cattle, Adami and Abbott¹ used the same methods in human cases. By special staining methods they demonstrated great numbers of organisms in the livers of 5 human cases, and cultivated the organism in 4 cases. This organism was very minute, ovoid or coccoid in shape and grew in long chains. It manifested a confusing pleomorphism, but was identified as a strain of *Bacillus coli* by Adami's coworkers. On the strength of these findings, cirrhosis is discussed as an example of the mechanism called subinfection in Adami's volume on *General Pathology*.

Mallory¹² examined for bacteria the livers from 2 cases of juvenile cirrhosis and found slender bacilli, possibly *Bacillus coli*, in 1 of them. No cultures were made. He believed these cases were of infectious origin.



FIG. 1.—Case I. Juvenile cirrhosis, photograph of liver and spleen.



FIG. 2.—Case II. Juvenile cirrhosis, photograph of liver and spleen.

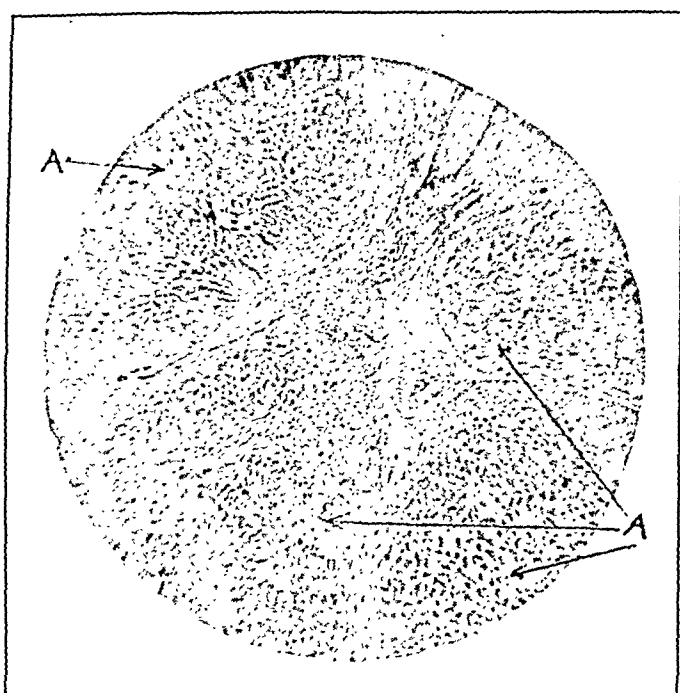


FIG. 3.—Case II. Liver, low magnification. Shows perilobular distribution of mature fibrous tissue. New fibrous tissue invading lobules where destruction of liver cells has occurred, as at A.

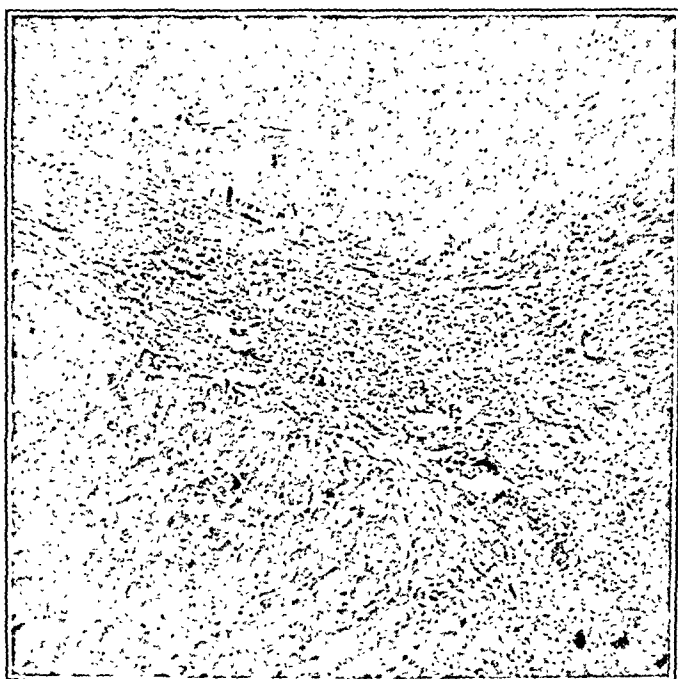


FIG. 4.—Case II. Liver, medium magnification.

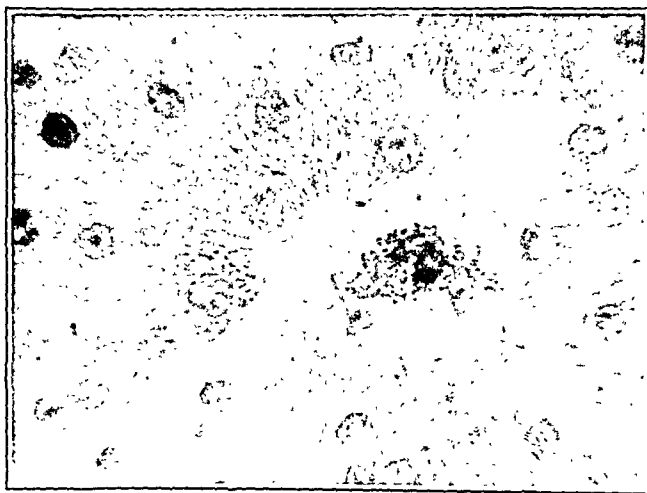


FIG. 5.—Case II. Liver, Gram-Weigert stain, high magnification. Degenerated and necrotic liver cells. Scattered cocci, and a large cluster in a group of necrotic liver cells.

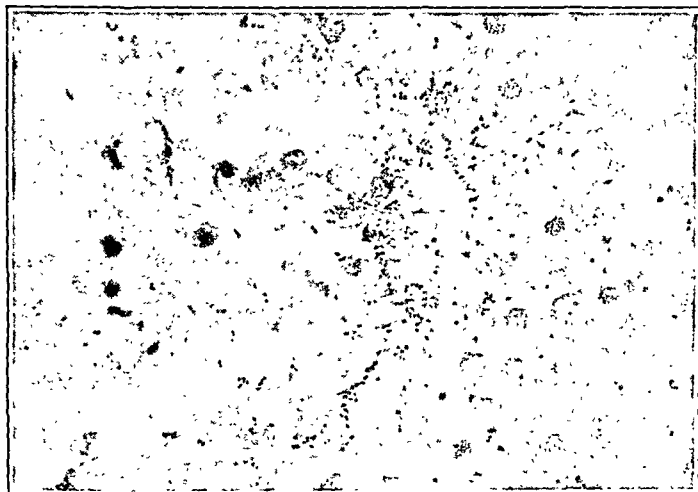


FIG. 6.—Case II. Spleen, Gram-Weigert stain, high magnification. Splenic cells mostly degenerated or necrotic; engorgement of blood spaces; numerous cocci.

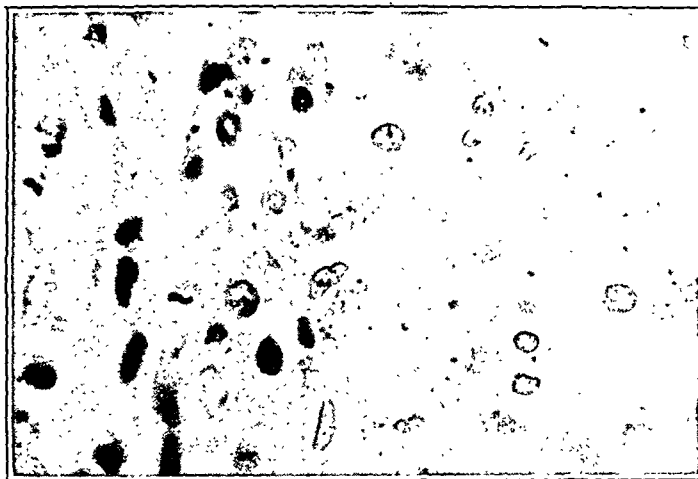


FIG. 7.—Case I. Liver, Gram-Weigert stain, high magnification. Degeneration and necrosis of liver cells; numerous scattered cocci.



FIG. 8.—Case I. Spleen, Gram-Weigert stain, high magnification. Degeneration of splenic cells, fibrosis, engorgement, numerous cocci.

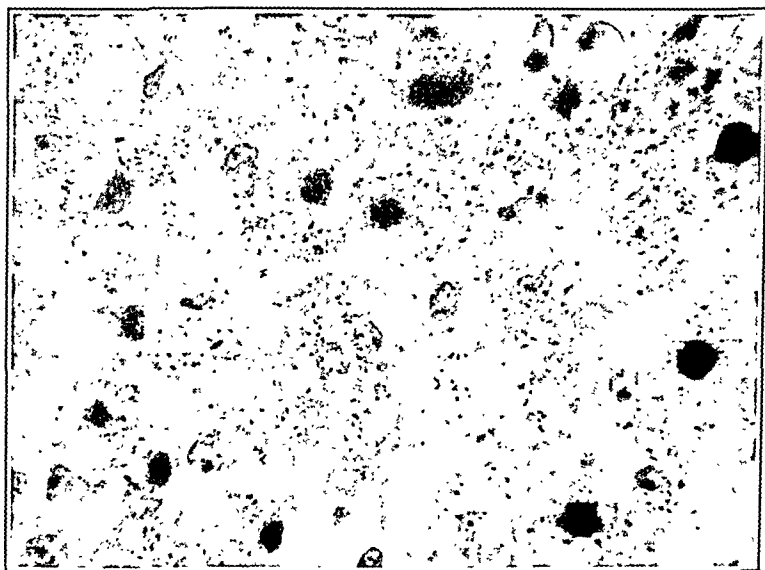


FIG. 9.—Liver of rabbit, killed seven days after a subcutaneous inoculation with hemolytic streptococcus, mixed with soft agar. This specimen was in fixative within five minutes after the rabbit was killed. Gram-Weigert stain, high magnification. Destruction of liver cells, congestion, numerous cocci.

Baginsky⁴ cultivated a streptococcus from the heart blood and from substance obtained by puncture of a cirrhotic liver in 1 case.

Folger,⁸ in 1 case, found streptococci in the liver; no cultures were made.

Weaver¹⁶ produced cirrhosis in guinea pigs by injecting *Bacillus coli* into the portal circulation. Hektoen⁹ reported similar experiments.

Notwithstanding the accumulated evidence suggesting infection as a cause, a thorough bacteriologic study of cirrhosis has not been made. The instances are rare in which bacteriologic examinations of any kind are recorded in either clinical or postmortem reports. The author is attempting such a study, and the following results are of the nature of a preliminary report:

Case Reports. CASE I.—The patient, a girl aged twelve years, had no significant history except the indefinite mention of childhood diseases. Her symptoms were weakness, nosebleed and vomiting of blood. The skin was icteric, and the spleen greatly enlarged. Blood examination showed hemoglobin, 35 per cent; red cells, 3,500,000; white cells, 18,000, of which 60 per cent were polymorphonuclear and 40 per cent lymphocytes. Death occurred twenty-four hours following admission. The provisional diagnosis was Banti's disease.

Postmortem examination (Dr. B. L. Crawford) showed a spleen which was rough and fibrous and had irregular thickening of the capsule. The follicles could not be seen. The spleen weighed 930 gm. (Fig. 1). The liver was pale, shrunken, irregular, hard and nodular. Bands of fibrous tissue surrounded islands of liver cells. It weighed 980 gm. There was no ascites. Chronic hyperplasia of the spleen and chronic atrophic cirrhosis were the chief gross pathologic conditions.

On microscopic examination, the liver presented the usual picture characteristic of atrophic cirrhosis. The spleen was fibrotic; the pulp and follicles showed a decrease in cellular elements.

Sections of liver and spleen were stained by the Gram-Weigert (Figs. 7 and 8) method for demonstrating bacteria. Both the liver and spleen contained large numbers of cocci occurring in pairs, short chains and irregular groups.

The postmortem examination had been done too long before for cultures to be of value.

CASE II.—A white boy, Joseph S., aged fourteen years, was rather small for his age. He was one of a family of 14, 8 of whom were living. One sister died of atrophic cirrhosis at the age of thirteen years with clinical features similar to those presented in this case. Some weeks subsequent to Joseph's death his brother, aged twelve years, was brought to the hospital with a greatly enlarged abdomen and essentially the same clinical features as Joseph had shown. His parents removed him from the hospital before clinical studies were completed. Joseph had had diphtheria but the parents gave no account of other infection. The younger brother was stated to have had scarlatina. The use of alcohol was denied both by the boy and the parents.

The condition began insidiously with no pain nor distinct malaise. Lassitude and swelling of the abdomen were first noted. Examination showed a greatly distended abdomen. The liver and spleen were greatly enlarged. No ascites was present on admission but developed in large quantities later. The hemoglobin was 47 per cent, the red cells 2,700,000 and the leukocytes

2600. There was no history nor evidence of syphilis. Blood Wassermann test was negative for each of the parents. The patient's blood was anti-complementary. The temperature ranged from 97.6° to 100° F.; on one occasion it rose to 102.4° F. The urine was concentrated and dark in color. Otherwise no abnormal urinary findings were noted. Slight icterus developed shortly before death. There was a slight tendency to bleed from insignificant injuries but no spontaneous hemorrhages. The course was progressive, ending in death ten weeks after the abdominal swelling first developed. No clinical diagnosis was made.

Postmortem examination (Dr. B. L. Crawford) showed slight icterus of the skin, prominence of superficial veins, distended abdomen and edema of the scrotum and legs. There was an excess of clear fluid in the pericardial, pleural and peritoneal cavities. The lungs were congested and showed early bronchopneumonia. The lymph nodes near the hilus of the liver and pancreas were about 2 cm. in diameter. They were soft and had a grayish-red color. The kidneys were slightly swollen and were pale.

The spleen weighed 1120 gm. It was smooth, firm and deep red, slightly mottled. It did not bleed when cut. Microscopically there was almost total absence of cells in the splenic pulp and of lymphocytes in the follicles. There was slight proliferation of fibrous tissue. The splenic sinuses were distended with blood and there was widespread recent necrosis of the cells of the splenic pulp.

The liver weighed 1330 gm. It was uniformly enlarged, pale yellow in color and the surfaces were roughened and nodular giving it a typical "hob-nailed" appearance. The nodules varied from 2 mm. to 1 cm. in diameter. The liver was hard and cut with marked resistance. The cut surfaces showed a marked proliferation of connective tissue surrounding small yellowish nodules of liver substance. Microscopic examination showed a marked cirrhosis, which differed from atrophic cirrhosis as seen in adults, only in that the process seemed more recent and more active than that usually seen in adult cases. Three processes marked the condition: Degeneration, necrosis and disintegration of liver cells; proliferation of liver cells and of bile ducts; abundant widespread proliferation of fibrous tissue, perilobular in distribution, but invading the lobules, where necrosis of liver cells was most marked. There was a moderate cellular infiltration, consisting mostly of lymphoid cells together with a small percentage of polymorphonuclear cells. These features strongly suggest a chronic infectious process, in which the inflammatory reaction shows proliferative rather than exudative features.

This case presented suitable opportunity for bacteriologic study postmortem. A small bit of liver was excised aseptically. Scrapings from it were streaked on blood agar, suspended in columns of melted agar and planted in broth. After twenty-four hours' incubation, there were hundreds of minute, grayish colonies on the blood-agar plates. Each colony was surrounded by a wide zone of hemolysis. No other type of colony was present. The columns of agar contained very numerous, small, grayish colonies throughout. The broth cultures were uniformly slightly turbid. Microscopic examination of each of these showed streptococci in perfectly pure culture. No other organism grew in any of the cultures.

Paraffin sections of the liver, stained by Gram-Weigert's (Fig. 5) method, showed numbers of cocci occurring in pairs, short chains and irregular clumps. The liver cells containing these cocci showed

advanced degeneration, many were necrotic and were undergoing disintegration. This condition was found diffusely throughout all parts of the liver. Sections of the spleen, stained by Gram-Weigert's (Fig. 6) method, showed likewise great numbers of streptococci, the distribution of which was not so diffuse, but rather tended to localization in small clumps. No bacilli nor other organisms were found in these sections.

It seems improbable that the streptococci found in the liver and spleen were the result of postmortem contamination for the following reasons:

Their presence in numbers was accompanied by necrosis of liver cells and more active cellular response than where the cocci were not so numerous. This would indicate their presence during life.

The streptococci were cultivated in pure culture and in large numbers. A postmortem invasion of the liver would probably have consisted of motile bacilli from the bowel tract. Such organisms appear earliest as postmortem contaminants.

The streptococci were found equally numerous in sections from the upper surface of the right lobe, the central portion and the portion adjacent to the colon. Postmortem spread of organisms would be most numerous adjacent to the bowels.

No organisms were found in sections of the kidney cortex, although sections taken from the anterior surfaces were examined. A post-mortem spread of bacteria should involve the anterior portions of the kidney, at least as early as it would the entire substance of the liver and spleen.

Cultures of the heart's blood taken at autopsy remained sterile. This would be unlikely if either postmortem contamination or terminal septicemia were the occasion for the widespread distribution of streptococci in the liver and spleen.

Rabbits were inoculated immediately with the hemolytic streptococcus cultivated from the liver. Some received intraperitoneal injections of the centrifugalized sediment from broth cultures; others received similar sediment intravenously. In others, sediment containing streptococci was mixed with melted agar and injected subcutaneously. The latter method was designed to produce a slower absorption of the bacteria into the animal's circulation. It was an attempt to produce a chronic focus of infection from which invasion of the system might take place continuously.

The histories of the first four are given in detail. The remaining eight had exactly similar features following the inoculation except that in three there was an intercurrent infection of rabbit pneumonia, which was a factor in causing the death.

Rabbit No. 1, received 2 cc. of broth, very rich in bacteria, intraperitoneally. He became sick, ate very little, lost flesh and died four days after the inoculation. Postmortem examination was made within thirty minutes of death. The muscular tissues were pale; the liver much enlarged and very

dark red, the gall bladder greatly distended. The kidneys, spleen, adrenals, heart, lungs and joints appeared normal. Tissue or fluid from each of these areas was cultured. A pure culture of hemolytic streptococcus was obtained from the heart's blood and from the spleen and liver. Cultures made from the kidney, bile, muscle, joint fluid and peritoneal washings remained sterile.

Rabbit No. 2, inoculated subcutaneously with streptococci in agar, developed redness and swelling at the site of inoculation. Two days later he seemed slightly sick, slightly inactive, but continued to eat normally. Five days after inoculation he was again apparently normal and remained so until the eighth day when he was killed and examined. There was a localized abscess 1 cm. in diameter, at the site of inoculation. The liver was very large and dark red. The other organs and tissues appeared normal. Cultures were made as in rabbit No. 1. The streptococcus was recovered from the liver and from the subcutaneous abscess. It was not present in the cultures from the other sites. (See Fig. 9 for condition of liver.)

Rabbit No. 3, inoculated by subcutaneous injection of agar behaved similar to rabbit No. 2 and was apparently normal six days after the inoculation. He died and was examined ten days after inoculation. There was a subcutaneous abscess about 1.5 cm. in diameter at the site of the agar injection. The liver was dark red but not enlarged. The pericardium was distended with about 5 cc. of clear fluid. The peritoneum contained about 15 cc. of clear fluid. Cultures were made as before. The streptococcus was recovered in pure culture from the liver, the pericardial fluid and from the site of the agar injection. It did not appear in cultures from other sites.

Rabbit No. 4, was injected intraperitoneally with about 4 cc. of the original broth culture from the boy's liver. He was distinctly sick for several days but gradually recovered. Seven days later he was apparently normal except for lameness in the left leg, the knee joint of which was swollen and tender. Two weeks after inoculation he was killed and examined. The peritoneum showed no evidence of inflammation. The liver was very large and dark red. A local abscess was present in the mediastinum and the left knee was swollen and contained purulent material. All other structures appeared normal. Streptococci were recovered from the liver, mediastinal abscess and joint. Cultures from other sources including the peritoneum showed no growth.

The details and results of the experiment on rabbits are given in tabular form for the sake of brevity.

It will be seen from an inspection of the tabulated results from this group of rabbits that in 11 of the 12 animals the inoculated organism was recovered from the liver. The rabbit, No. S5, died at night and examination was made a number of hours later. Post-mortem contamination of the organs in this rabbit made it impossible to determine accurately the presence or absence of the inoculated organism. Infection of the liver in these rabbits occurred regardless of the route or site of the inoculation. It was found also in the spleen in 5 of the rabbits. This may be significant in view of the fact that juvenile cirrhosis appears to be a splenohepatic disease rather than purely hepatic. Streptococci were demonstrated microscopically in the spleens of the human cases studied.

The fact that generalized infection and death did not occur regularly even when large numbers of streptococci were injected intravenously, indicates that the virulence of this particular strain

was low. Such a strain is well adapted to produce chronic infections. None of the rabbits in this experiment were allowed to live long enough for cirrhotic changes to occur. Experiments are being continued under conditions suitable to determine the effects of chronic infections with this streptococcus. Such results as may be obtained will be the subject of a later report.

RESULTS OF ANIMAL INOCULATIONS.

Rabbit.	Inoculation.	Termination.	Days.	Streptococcus recovered by culture from:					
				Liver.	Spleen.	Kidneys.	Blood.	Peritoneum.	Other sites.
S 1 .	Peritoneal	Streptococcus infection	3	+	+	-	+	-	-
S 2 .	Agar, subcutaneous	Killed	6	+	-	-	-	-	Subcutaneous abscess.
S 3 .	Agar, subcutaneous	Streptococcus infection	10	+	-	-	-	-	Pericardium.
S 4 .	Peritoneal	Killed	13	+	-	-	-	-	Mediastinal abscesses, joint.
S 5 .	Peritoneal	Epidemic pneumonia	20	±	±	±	±	±	±
S 6 .	Peritoneal	Streptococcus infection	2	+	+	-	-	+	-
S 7 .	Intravenous	Epidemic pneumonia	15	+	-	-	-	-	-
S 8 .	Intravenous	Epidemic pneumonia	10	+	-	-	-	-	Pericardium.
S 9 .	Intravenous	Streptococcus infection	5	+	+	-	+	-	Gall bladder.
S10 .	Intravenous	Killed	6	+	+	+	+	-	-
S11 .	Intravenous	Killed	6	+	-	-	-	-	-
S12 .	Agar, peritoneal	Streptococcus infection	4	+	+	-	-	+	Mediastinum; lung; pericardium.

EXPLANATION: Under the termination "killed" the rabbit was always first anesthetized. The symbols + and - indicate the presence or absence of the organism in cultures from the organ. The symbol ± indicates indeterminate result.

Sections from livers of the rabbits showed extreme degeneration and destruction of liver cells. In many cases the cells were far advanced toward dissolution and no cells of normal appearance were to be found. Sections stained by Gram-Weigert's method showed very numerous cocci (Fig. 9). In some, these were diffusely distributed throughout the sections; in others there was some tendency to localization.

A remarkable feature was the deficiency of inflammatory response to the infection. Leukocytes were absent, or very few were present, even in areas where injury to the liver cells was extreme and where many cocci could be seen.

Conclusions.—Evidence from collected cases indicates that juvenile cirrhosis is a combined disease of liver and spleen.

The presence of streptococci in the liver and spleen was determined in 2 cases of atrophic cirrhosis occurring in children of school age.

The streptococci cultivated from the liver of one case showed a definite tendency to infect the liver in animals.

The histologic changes present in cirrhotic livers are such as would result from a diffuse infection of long duration.

Chronic infection of the liver should be regarded among the important causes of cirrhosis.

NOTE.—The author acknowledges indebtedness to the Medical Staff of Jefferson Hospital and to Dr. Crawford, pathologist, for their hearty coöperation in this study.

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SCLEROSING TREATMENT OF VARICOSE VEINS BY CHEMICAL IRRITANTS.*

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THIS common, distressing, unaristocratic malady has been successfully treated by the intravascular injection of sclerosing solutions, in Europe since 1911. Pravatz¹ and others from 1851 to 1853 tried the injections of blood coagulating solutions such as perchlorid

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of iron, alcohol, tincture of iodine and Pregel's (isotonic iodine) solution. The severe reactions, infections and fatalities soon discouraged the pioneers in this field. In 1894, DeLore² showed that success was due to the reaction in the vein wall and not due to the coagulation of the blood. Then noncoagulating or anticoagulating solutions were tried with more success. The variety of the agents used testifies to the dissatisfaction experienced with first one and then another sclerosing agent. Not one of the agents met the ideal requirements, namely, certain action without unpleasant necessary symptoms. The agents used include mercuric chloride, mercuric diiodide, sodium chloride, argochrom, pyoktannin, quinine urethane, sodium bicarbonate, sodium salicylate, and the like. In 1927, Kausch³ introduced the use of invert sugar, which possesses most of the advantages with but few of the disadvantages of other sclerosing agents. Professor Nobl in some 10,000 injections in some 3400 cases, without a fatality, has proven the worth of invert sugar in the production of phleboscclerosis.

The varices herein considered are the enlarged tortuous external veins of the lower extremity. The cause most generally accepted is a combination of a hereditary or constitutional predisposition with the exciting cause, such as hydrostatic pressure from prolonged standing, heavy lifting, or any condition as abdominal tumor or pregnancy that will cause increased intraabdominal pressure. Halion believes the fundamental cause to be valvular deficiency in the upper portions of the vein. The experiments of Trendelenburg and Perthe, and as verified by Magnus⁴ and Jentzer, have shown that there is a flow of blood in the peripheral direction when varices are present. This retrograde flow explains the paucity of emboli and the rapid formation of ulcers. The blood normally flows to the heart because of pressure of blood flowing from the capillaries. The deep veins suffice for the removal of blood from the tissues. Loss of function in the varicose veins results in dilatations, engorgement, trophic skin disorders (such as ulcers and eczema), thrombophlebitis and hemorrhage; and gives rise to the symptoms of debility, fatigue, pain and leg cramps; and causes an unsightly appearance. Successful treatment results in the permanent obliteration and complete disappearance of the enlarged veins, and within a short time in an improvement of the previously disturbed circulation. Patients regularly report that the heaviness and fatigue disappear and they feel more efficient.

The delayed acceptance of this method of treatment by the medical profession has been due to the fear of emboli. A knowledge of the process of sclerosis should dispel this fear because the danger is chiefly theoretical. Animal experiments by Doerffel,⁵ Regard⁶ and Bazelis,⁷ verified by Binet and Verne, have shown that an adherent clot is formed in veins injected with sclerosing agents. Their detailed macroscopic and microscopic studies of treated veins from



FIG. 1.—Mrs. A. O. No. 16748.
July 1, 1927. (Before.)



FIG. 2.—No. 16748. April
1, 1928. (After.) Three injections
Invertose; 3 injections sodium chlorid, 20 per
cent.

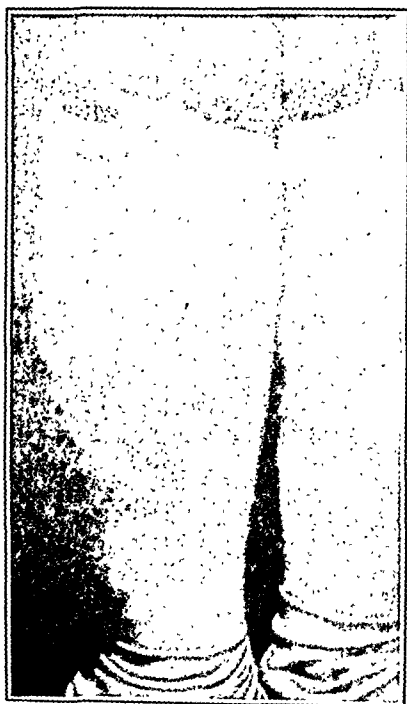


FIG. 3.—Mrs. F. A. Y. No. 4226.
November 8, 1927. (Before.)



FIG. 4.—No. 4226. January 25,
1928. (After.) Eight injections In-
vertose.



FIG. 5.—Mrs. S. No. 25263. June 23, 1927. (Before.)

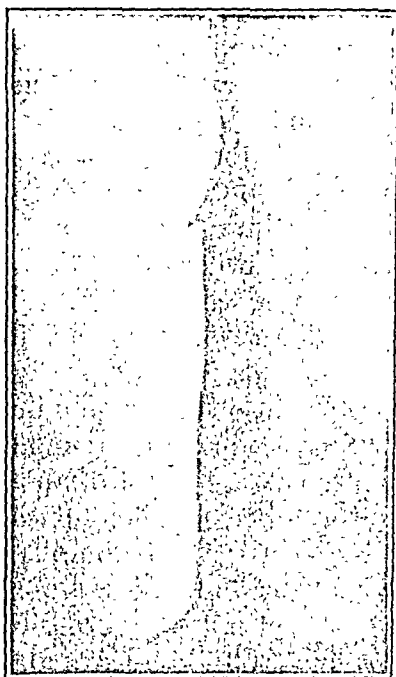


FIG. 6.—No. 25263. October 12, 1927. (After.) Seven injections Invertose.



FIG. 7.—Mrs. C. No. 25036. May 11, 1927. (Before.)



FIG. 8.—No. 25036. October 11, 1927. (After.) Nine injections Invertose; 1 injection 20 per cent sodium chlorid. Note scar of slough after injections of sodium chlorid.

one to fifteen days after injection are well worth study in detail. Briefly, they show that the sclerosing solution acts as a chemical irritant to the intima, which results in a marked swelling and desquamation of endothelial cells, which is followed by a trabecular deposit of fibrin and blood platelets. Two factors are active in bringing about obliteration: (a) Unusually intensive proliferation of the intima building a trabecular structure in the lumen; (b) secondary formation of thrombi (excretory thrombus) induced by irritation of the intima, while in a purely mechanical fashion a stagnation thrombus forms in the meshes of the intima. Organization proceeds and progressive retraction takes place, resulting in a transformation of the vein into a thin fibrous strand, in which only a few muscle fibers are demonstrable. Meisen's⁸ patient, who came to autopsy as a result of an accident while under treatment, showed the thrombus so adherent that it could not be expelled by pressure on the vein. The thrombus through its main extent had grown fast to the vein wall. Vessel offshoots showed adhesions with masses of connective tissue. Thrombus masses everywhere were fixed to the vascular wall by means of connective tissue. In view of these findings it is obvious why embolic phenomena have been rare.

While in Europe, one of us (R. C. L.) was so impressed with the good results from the use of invert sugar (calorose) that it was decided to use this form of treatment. Difficulty in obtaining the foreign product led to the preparation and use of a domestic product (invertose). All of the cases reported in this paper have been treated with this invert sugar solution. In some of the cases one or more veins have been treated with 20 per cent sodium chlorid solution for purposes of comparative study. We prefer the invert sugar because it is practically painless, nontoxic and sloughing does not occur following an accidental injection outside the vein. We have noted that the formation of thrombus proceeds more slowly but organization becomes complete. Canalization and recurrence is rare. The reaction in and about the vein (periphlebitis) is less likely to develop. This increases the factor of safety. We have noted no general reactions.

Technique. An effort is made to bring the sclerosing solution into contact with the intima in a maximum concentration. While the patient stands erect, the point of injection is selected and marked. The site should be as high up the vein as possible but never above the level of the lower third of the femur. In ulcer cases the practice is to first treat the veins apparently responsible for the ulcer. The patient then lies prone on the table and the skin about the site of the injection is sterilized as for any intravenous therapy. The blood is then gently "milked" from a section of the vein for a distance of a few centimeters above and below the site selected for injection. The assistant then applies firm pressure with the fingers at two points, one above and one below the site of injection, to keep the vein partly emp-

tied of blood. This firm pressure is maintained during the injection and for five minutes (by the clock) after the injection. A needle, 18- to 24-gauge, attached to a sterile glass syringe filled with the solution is carefully inserted into the vein at the site previously selected and marked. Blood is aspirated into the syringe to make certain the needle is well within the vein. The solution is then injected rapidly into the partly emptied vein until there is moderate distention. The amount required will vary from 5 to 20 cc., depending on the size of the varix. The moderate distention of the vein with the needle *in situ* is maintained for fully five minutes to properly affect the intima. A small thick gauze pressure dressing is applied over the treated area as the pressure is released and the needle withdrawn to prevent leakage from the vein. Adhesive strips are applied to maintain the pressure dressing for a period of two or three days. Where large, prominent, highly elevated veins have been treated, it is well to apply a pressure pad over the entire course of the vein, especially if the contraction phenomenon after injection has been noted. This pressure is maintained for a week or more until sclerosis is complete. The elastic bandage is applied from ankle to thigh. This hastens the disappearance of the vein. The patient is instructed to get up and go about as usual to attain best results.

Summary of Cases Treated. We wish to report our experience with 96 cases, 23 males, 73 females, average age forty-five years. The average number of injections necessary for each case was between 5 and 6. Ulcers were present in 20 cases, eczema in 8, and extensive edema in 8.

Some 63 injections of 20 per cent sodium chlorid solution were used in 28 patients. Sixty injections were followed by severe cramps, 4 patients fainted. In only 3 injections were the cramps slight. Ten of the injections were followed by periphlebitis. Failure to obtain sclerosis after the first injection of salt solution was noted several times. In one case no sclerosis was obtained after repeated injections of salt solution (as well as mercuric chlorid and invertose). Four injections were followed by tissue necrosis, three of the sloughs being attributed to accidental injection of the salt solution outside of the vein, and one from leakage through the needle puncture after injection.

Some 546 injections of invertose, 40 to 60 per cent, were made on 96 patients. Four of these were followed by severe cramps, 19 by moderate cramps, 231 by slight feeling of tightness, discomfort without actual pain and 292 without discomfort of any kind. Failure to obtain sclerosis after injection was noted in 17, and partial failure or slight sclerosis was noted after 56 injections, due to hyposensitive intima. Fifteen injections were followed by varying grades of periphlebitis. Although in several instances the accidental injection of 2 to 5 cc. of invertose outside of the vein was noted, but one slough followed, that in a case of a very old lady with unhealthy looking

skin. In this case, a small area of dry gangrene appeared along the course of the injected vein. In 4 cases, an extensive sclerosis was noted along almost the entire course of the internal saphenous magna, probably due to a hypersensitive intima.

The following complicating conditions were noted: Obesity in 12 cases, hypertension in 14 cases, diabetes in 2, nephritis 1; decompensated heart in 1, previously operated 7, and lues in 1 case; all of which were treated with good results. One case had extensive scars following burn of the legs, recurrences were noted after treatment. Two cases previous to treatment suffered from phlebitis. It was interesting to note that the areas of thrombosis which followed the phlebitis became recanalized while areas of veins obliterated by the sclerosing solutions remained closed. In 1 case of diabetes with eczema, Mrs. J., aged fifty years, we noted an exacerbation of the eczema after injections of invertose.

The results have been tabulated after six months observation: Unknown: 2 cases; fair in 2 cases; good in 92 cases; recurrence in 2 cases (incompletely treated).

Complications. Periphlebitis may be extensive and distressing. It differs definitely from the usual periphlebitis in that it is not due to an infection, there is no fever, the pain is not so continuous, and only the superficial treated vein is involved. It is usually caused by the injection of large amounts of strong solutions into closely adjacent veins. The treatment is rest and local applications of heat. Recovery is permanent and results are satisfactory.

Embolism is usually fatal. Few cases have been reported. Two cases, those of Meisen and Lomholt,⁹ were admittedly due to large and hurried injections of 20 per cent sodium chlorid. One, that of Hammer,¹⁰ followed an overdose of mercuric chlorid to a nephritic subject. Another, that of McPheeters,¹¹ died of pulmonary embolism two weeks after treatment with sodium chlorid, hence not definitely a result of treatment.

Accidental perivascular injection results in the development of slow healing slough with all concentrated strongly irritating solutions except invert sugar, where a painful somewhat indurated area obtains, and disappears in a few days or a week.

Nonsclerosis will disappoint the physician and the patient at times. Linser believes that it is always due to incorrect technique or insufficient strength of the solution, but an analysis of his cases show the occasional failure to obtain sclerosis even when using 40 per cent sodium chlorid. Cases of nonsclerosis have been recorded with all of the agents. We lean to the view of Revinovsky that individual idiosyncrasy is responsible for the occurrence of nonsclerosis. In some cases the intima seems unduly tolerant to the solution, or develops increased tolerance to the solution during the course of the treatment. Repeated injections in the same area every two days will usually bring about a sclerosis. Cases tolerant to one solution may be sensitive to other solutions.

Various men have reported the following contraindications to the use of this method of treatment: Cases of plethora with hypertension; cardiopathy, cardiorenal disease; pregnancy, large abdominal tumors; phleboliths, deep phlebitis, and recent superficial phlebitis.

Conclusion. We believe that the method of induced sclerosis is the method of choice in the majority of cases of varicose veins, and that invert sugar is the preferable agent for inducing the phleboscclerosis.

We believe this method of treatment is better than surgery for the following reasons: The danger of embolism is less; the cost to the patient is less; the amount of pain is less; there is no scar formation; recurrences are less frequent; and the patient is not confined to bed.

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EXPERIMENTAL STUDY OF THE EFFECTS OF STIMULATION AND SECTION OF THE VAGAL INNERVATION TO THE BRONCHI AND THEIR POSSIBLE RELATION TO ASTHMA.*

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THE chief characteristic of asthma is the recurrence of paroxysmal attacks of respiratory dyspnea which last a variable length of time, frequently until the action of some drug affords relief. The suddenness of the onset and the course of the attack suggest, as the under-

* Work done in Division of Experimental Surgery and Pathology, The Mayo Foundation. Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1928.

lying mechanism, spasm of the bronchial musculature in response to some stimulus. It is fairly well established that the constrictor fibers to the bronchi travel by way of the vagi. It is also generally accepted that there are cases of reflex asthma. Accepting these two factors, and granting that bronchial spasm plays a large part in the production of the attack, one might assume that the stimuli that reach the lung and produce the asthmatic attack probably travel by way of the vagi.

The literature supports the theory of reflex asthma. Experimentally Carlson and Luckhardt showed contraction of the lung in the turtle resulting from rubbing of the posterior nares. Sluder reported a case in man in which an attack of asthma could be produced at will by the application of irritants to the sphenopalatine foramen. A great many cures of asthma have also been reported following correction of abnormal intranasal conditions. Abbott reported cases of ethmoiditis and asthma in which the asthma was relieved when the ethmoiditis improved and was made worse with the return of the ethmoiditis. Cases reported by Henderson and De Jong, in which cures of asthma followed operations for anal prolapse; chronic appendicitis, and pelvic abnormalities, suggest that asthma may be dependent on pathologic processes other than those in the nose.

Much benefit has resulted from the study of the hypersensitive cases of asthma in relation to anaphylaxis. Coca pointed out, however, a difference between atopic manifestations (asthma and hay fever) and anaphylaxis, but stated that both antibody and atopic reagin may exist simultaneously. Much more remains to be learned about the way in which foreign-protein sensitization causes paroxysmal bronchial spasm. Two obvious mechanisms suggest themselves: one that the sensitized bronchiolar musculature, on coming in contact with antigen, fixes this very much like the sensitized uterine muscle fixes antigen *in vitro*,⁶ and another that the bronchiolar spasm is essentially a reflex by way of the vagi, the sensory stimulus to this reflex being a local reaction in some part of the body, where generalized hypersensitivity exists (so-called Arthus phenomenon).

The first hypothesis has been rather widely discussed in the literature, but the second has not been given the attention it seems to deserve. Cases of hay asthma, on the latter hypothesis, could quite possibly be the result of a vagal reflex, by way of the fifth nerve, ending in the eyes and nose. Sluder reported a case of asthma which would be difficult to explain except on a reflex basis. A patient who was sensitive to the pollen of ragweed suffered from an attack of severe asthma in midwinter when pollen was introduced into the sphenoidal sinus; the attack was stopped at once by the intrasphenoidal application of cocain.

This study was undertaken to determine whether a physiologic basis existed for a reflex mechanism in certain cases of asthma. An attempt was made to determine whether changes could be produced

in the lungs of experimental animals by various methods of stimulation of the vagi, similar to those found in lungs of asthmatic patients.

If certain cases of asthma are due to stimuli reaching the lung by way of the vagi, relief should result from a method of treatment

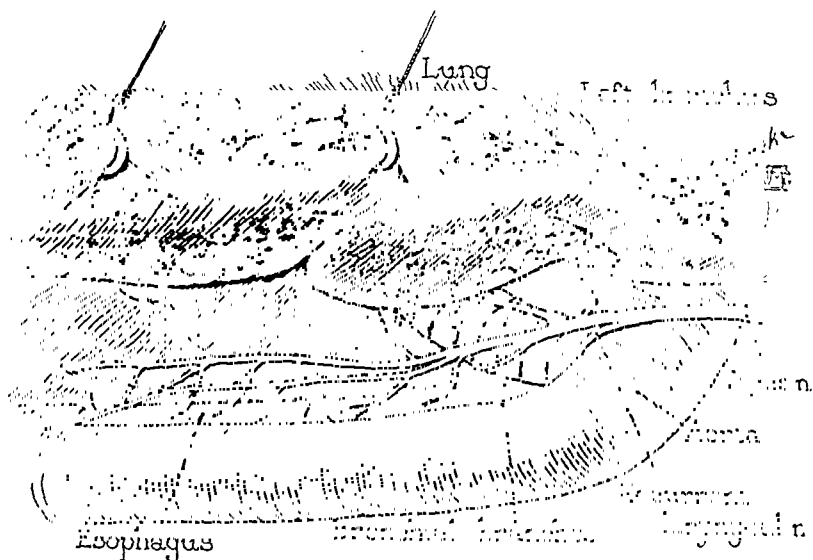


FIG. 1.—The course of the left vagus and its bronchial branches in the posterior mediastinum of man.

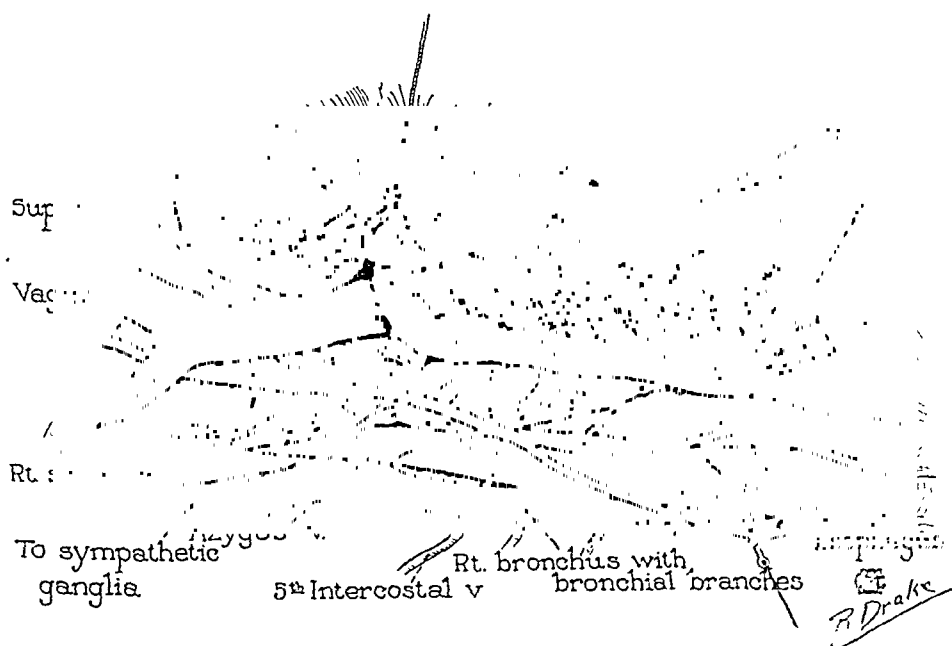


FIG. 2.—The course of the right vagus and its bronchial branches in the posterior mediastinum of man.

which would interrupt the pathway of these stimuli. Dissection of the bronchial branches of the vagi in the posterior mediastinum of a human being was therefore made (Figs. 1 and 2), and the effects of their section and evulsion studied in a series of dogs.

Methods. Guinea pigs, dogs and one monkey were used. For recording contraction of the bronchi following vagal stimulation in the dog, chloral hydrate anesthesia was induced, and both vagi were isolated in the neck. With the aid of a bronchoscope, a small rubber



FIG. 3.—Lower lobes from the lungs of a guinea pig whose right vagus had been stimulated with resultant emphysema of the corresponding lung.

balloon, tied to a brass tube, was inserted snugly into a bronchiole of the left lower lobe. The opposite end of the tube was attached to a recording chloroform manometer. To obviate secondary



FIG. 4.—A bronchiole from the right lung of a guinea pig whose right vagus had been stimulated. The lumen is obliterated and there is apparent contracture of the musculature.

changes as a result of respiratory alterations following stimulation of the vagi, the thorax was opened. When respiratory activity had ceased the vagi were stimulated.

In the guinea pig, a special method was devised for demonstrating

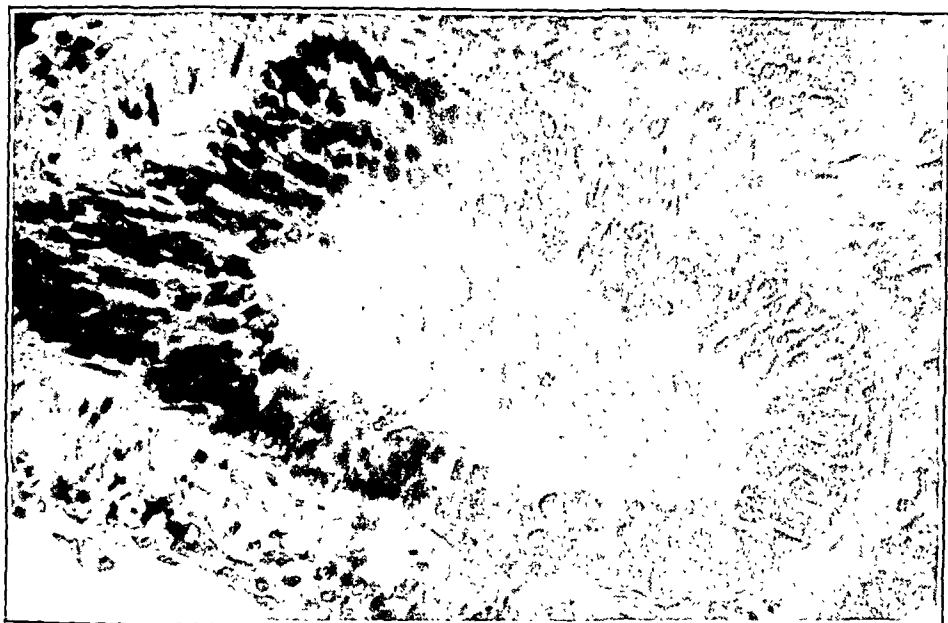


FIG. 5.—A large bronchiole from the lung of a guinea pig whose right vagus had been stimulated, showing more clearly the content of the bronchial lumen consisting chiefly of secretion.

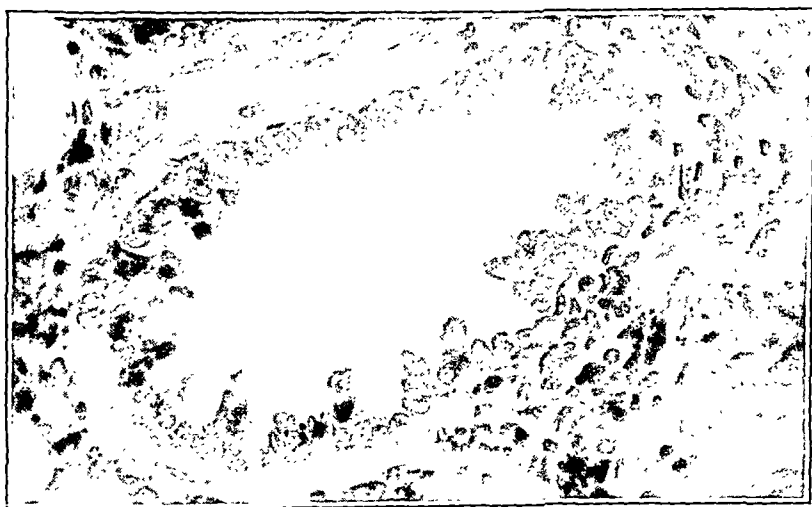


FIG. 6.—A bronchiole from the lung of a control animal treated in the same manner as the other animals except that the vagus was not stimulated. There is some irregularity in the epithelial outline and a small amount of content in the lumen. }



FIG. 7.—A bronchiole from the lung of a guinea pig whose vagi had been mechanically stimulated by sutures placed about them. The epithelium is stained poorly and shows definite changes with an irregular outline. There is an eosinophil in the bronchial lumen besides secretion and other cells.

bronchiolar spasm; this consisted essentially in immediate fixation of the animal in formalin after unilateral vagal stimulation under ether and later in comparison of the volume of the two lungs. In some guinea pigs the effects of simultaneous mechanical stimulation of the vagi were studied. For this purpose, tracheotomy was performed under ether anesthesia in order to rule out the possibility of dyspnea from paralysis of the muscles supplied by the recurrent laryngeal nerve. A ligature was placed under each vagus, and the skin infiltrated with procain and sutured. After the animal recovered from the anesthetic, and was breathing freely, and rhonchi were not audible with the stethoscope, the vagi were stimulated by gentle motion of the ligatures under them, and then the ligatures were tied loosely over the nerves so that they were not injured.

The guinea pigs in another series were sensitized to a fresh extract of horse dander by intraperitoneal injection of 1 cc. of a solution made up as described by Ratner, Jackson and Gruehl, and a method developed whereby dry dander could be blown into the nostrils.

In a study of the effects of section of the bronchial branches of the vagi, eight dogs were operated on under intratracheal ether insufflation anesthesia and strictly aseptic technique. The posterior mediastinum was reached by the transpleural route and the bronchial branches of the vagus were sectioned close to this nerve and evulsed. The nerves of one side only were sectioned at the first operation; on the other side they were sectioned two or three weeks later when the animal had recovered.

Results. Electrical stimulation of the peripheral end of the left vagus in the neck of a dog after section resulted in well-sustained contraction of the bronchioles of the left lung. Electrical stimulation of the right vagus gave bronchiole contraction in the left lung which was approximately half that resulting from stimulation of the left vagus.¹¹ These results were repeatedly obtained in the same animal.

Electrical stimulation of the peripheral end of the right vagus in the neck of the guinea pig often caused emphysema of the lung, giving this an appearance similar to that seen in anaphylaxis. The opposite lung appeared normal. The changes in the lung following stimulation of the vagus could be observed readily by opening the thoracic cavity during stimulation. In other experiments, when stimulation was commenced, the animal was killed by bleeding from the vessels of the neck. The whole animal was immediately fixed in 10 per cent formalin. The lung on the stimulated side was often definitely larger (Fig. 3); in one case its capacity was 10 cc. as compared with 5 cc. for the opposite lung. The experiments were controlled by repeating them on guinea pigs without electrical stimulation of the vagus. One must conclude, therefore, that electrical stimulation of the vagus in a guinea pig can cause pronounced emphysema of the corresponding lung, although the result

was obtained in only two thirds of the experiments. Failure was partly because of unavoidable trauma to the nerve incidental to the isolation for stimulation, and also, the method of electrical stimulation was found to be important.¹⁴

Microscopic study of the emphysematous lung revealed that the alveoli were distended and the lumen in many smaller bronchioles was entirely obliterated (Fig. 4). The epithelium stained poorly, and had lost its definite outline. The larger bronchioles were also partially or completely filled with secretion (Fig. 5), and there were peribronchial and parenchymal areas of cellular infiltration.

Although these microscopic changes did not occur in the control animals to any great extent (Fig. 6), it was considered advisable to repeat the experiments on pithed and decerebrate animals in which, following vagal stimulation, the lungs were immediately fixed either by excising a piece of lung and dropping it into formalin, or by the intravascular injection of fixing fluid. These experiments afforded data similar to those obtained when the vagi were stimulated.

Simultaneous mechanical stimulation of the vagi in the manner outlined caused dyspnea at once in all the experiments. Breathing was slow and labored, and rhonchi were easily heard with the stethoscope. These changes lasted from fifteen to sixty minutes, after which the animal appeared normal. The same response was produced on repeating the stimulation. Following these observations the animal was killed. In one animal of the series, which was killed while showing a well-marked reaction, the lungs were found to be emphysematous. In animals that had been dyspneic for an hour or more following mechanical stimulation of the vagi, the lungs showed secretion and cells in the bronchial lumen, including a few eosinophils (Fig. 7). In the parenchyma of the lung close to the bronchiole were typical eosinophils, and cells with typical eosinophilic granules but with an atypical nucleus.

On mechanical stimulation of one vagus, rhonchi were also produced in the corresponding lung in all instances which persisted and were similar to those occurring when both vagi were stimulated. The rhonchi were less persistent and fewer in number in the opposite side.

When the exposed vagi of a monkey were stimulated mechanically by a ligature, rhonchi resulted, with but little or no dyspnea.

On introduction of dry horse dander into the nostrils of guinea pigs previously sensitized to this material, a reaction occurred in 75 per cent of the animals tested. In the most outstanding result there was sneezing and rubbing of the nose, which, along with the eyes, dripped clear watery secretion. This was accompanied by severe respiratory dyspnea and the presence of rhonchi. The result was less marked although definite in other animals. It lasted a short but variable length of time, and could be repeated. In two hypersensitive animals tracheotomy was performed and the trachea tied off so that the dander could not come in contact with the mucosa of

the bronchial tree. After recovery from the anesthetic, the animal reacted to intranasal dander in a similar manner to the other animals.

Of the eight dogs operated on, one died from accidental pneumothorax. The remainder are well and apparently normal in every way three to four months after operation. These results are in harmony with those reported by Boothby and Shamoff, who studied the late effects of section of these nerves on gaseous metabolism, gas exchange and respiratory mechanism.

Comment. Although the literature related to this problem will not be discussed extensively, reference should be made to the very suggestive observations of Carlson and Luckhardt on lung reflex in turtles. As I have mentioned, these investigators found that rubbing of the posterior nares caused contraction of the lung, and Sluder reported a case in which an attack of asthma could be produced at will by the application of irritants to the sphenopalatine foramen.

The results reported following electrical and mechanical stimulation of the vagi in experimental animals are similar to those reported by Ellis in regard to the lungs of asthmatic subjects after death from severe attacks of bronchial asthma. It is possible that these experimental data may have a clinical bearing.

Unquestionably there are cases of reflex asthma of intranasal origin and cases are also reported in which cure has resulted from the correction of pathologic processes elsewhere in the body.

The group of cases now classified as chronic bronchitis with asthma may include cases of hypersensitiveness in which the protein is not known, and also cases in which there is a reflex origin outside the lungs. Chronic bronchitis may act as a point of irritation, causing reflex bronchial contraction of the musculature in the manner experimentally studied by Larsell and Burget.

Cases of asthma resulting from a reflex mechanism are best treated by elimination of the lesion at the point of irritation. If this fails, however, it might be worth while on the basis of these studies to section the bronchial branches of the vagi in the posterior mediastinum, using the extrapleural approach.

Summary. Physiologic and histologic observations were made on dogs, guinea pigs and one monkey with regard to the symptoms and changes produced by various types of stimulation of the vagi in the neck. In many cases the resultant changes in the lungs, bronchial constriction, bronchorrhea, cellular infiltration, and emphysema were similar to that seen in asthma. The studies thus establish a physiologic basis for the reflex nature of certain types of asthma.

The course of the fibers involved is presented and it was found that untoward symptoms did not result from their section in the dog. These experiments form the basis for the suggestion that in certain types of intractable asthma posterior mediastinotomy, with section of the bronchial branches of the vagi, using the extrapleural approach might be considered.

Investigators, cases.	Age.	Calcium, mg.	Remarks.
Herzfeld. ¹⁶ 70 Verified by Billigheimer. ¹⁷	11.00	No variation with age.
Hess. ²⁰ Infants with mild rickets	7.50-13.00	100 cc. plasma.
Koechig. ²¹ 11 normal	10.30	
Jansen. ²² 120 pathologic cases	Normal in most infections, but in croupous pneumonia 8.6-9.3 (CaO).
Tschimber. ²⁴ Normal	9.30-10.00	
Anderson. ²⁶ 40 children	2 mo-11 yrs.	10.70	
Matz. ²³ Normal	16-43 yrs.	10.28	
Andersen. ²⁹ 38 normal	Under 45 yrs. Over 45 yrs.	10.70 10.40	
Wills. ³¹ 12 children	2- 4 yrs.	10.40	
Di Foutsin. ³³	18-51 yrs.	11.70	
Nohlen. ³⁴ 19 cases: Newborn Mothers	12.65 11.40	
Wyss. ³⁵ Men Women	12.00-16.50 11.00-12.60	No change with age.
Rosen and Krasnow. ³⁶ 50 medical students	11.60	
Armstrong and Hood. ³⁷ 101 neurologic patients	9.00-10.75	

The calcium content during pregnancy is still an unsettled question. Various authors have contributed information, but there is much disagreement among them (18, 19, 22, 25, 27, 30, 38 and 39). It is hoped that future work may help to solve this question.

Several methods of determining calcium have been used, such as the Wright, Lyman, de Waard, Tisdall and Kirth methods. The variations in results of different investigators may be attributed to slight differences in methods used. In spite of the great mass of work done, our questions were not answered satisfactorily by previous studies.

Results. These investigations were carried out on individuals as nearly normal as could be conveniently found at the various ages. The 7 to 17-year group was composed of children attending Lymanhurst School. These children were undernourished, but able to attend school regularly. Their homes were rather humble. Previous contact with open cases of tuberculosis and undernutrition made it advisable for them to be under constant observation at Lymanhurst.

The 18 to 28-year group was composed of students attending the University of Minnesota. Most of them were in excellent physical condition. The 29 to 39-year group contained several medical students, several members of the teaching staff, and some patients from the University Dispensary. The last came from such clinics as neurology, dermatology and internal medicine. All were up and about, and engaged in work.

The 40 to 50-year group included some attending physicians, and dispensary patients comparable to the previous group. The 51 to 61-year group contained some dispensary patients and some individuals who resided at Parkview Sanatorium. The latter were chronic cases, having such handicaps as decompensated hearts, arthritis and partial paralysis, but no acute infections. They were no longer able to work. The 62 to 72-year group included Parkview patients and dispensary patients, mostly from the ear and heart clinics. All above 72 years were of the same type.

The blood was drawn by venepuncture, about two hours after the last meal, in most cases. The blood was allowed to clot spontaneously and then centrifuged. Serum was used for the calcium determinations. Clark's³² modification of the Kramer-Tisdall method was used. In almost every case duplicate determinations were made.

The results for women will be given first: 141 were studied, ranging in age from 7 to 83 years. The results for the different age groups are presented in Table I.

TABLE I.—RELATIVELY NORMAL WOMEN.

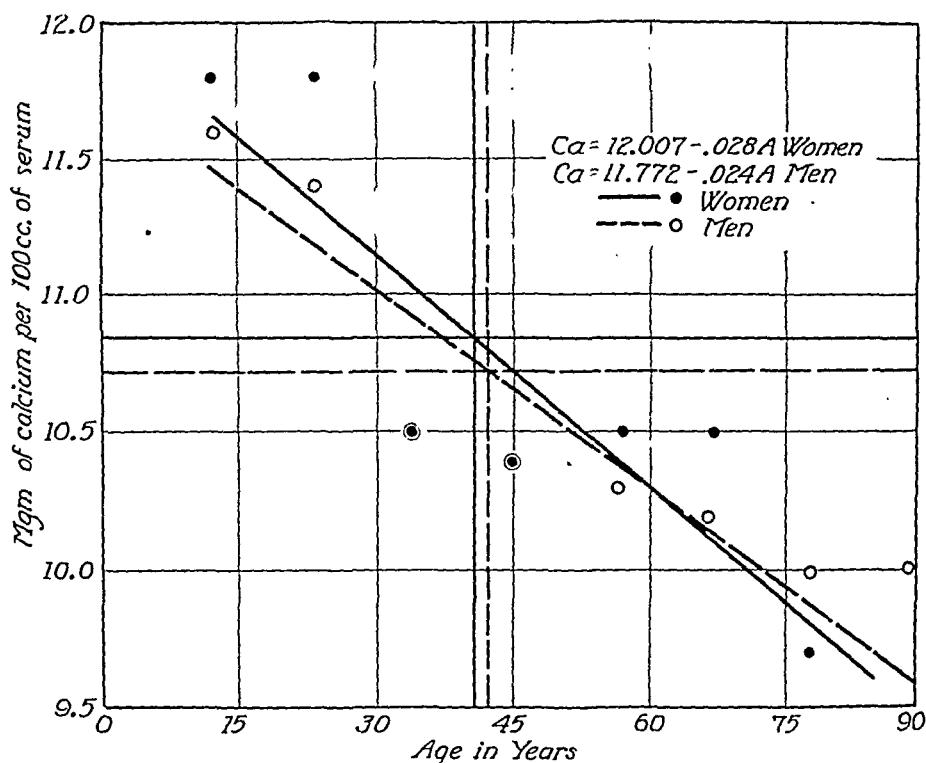
Number of cases.	Age group.	Calcium in mg. per 100 cc. of serum.		
		Minimum.	Maximum.	Average.
18	7-17	10.5	13.0	11.8
26	18-28	10.5	13.0	11.8
25	29-39	9.5	12.0	10.5
24	40-50	10.0	11.5	10.4
25	51-61	9.5	11.5	10.5
18	62-72	9.5	11.5	10.5
5	73-83	9.0	10.0	9.7

Examination of Table I reveals a decrease in calcium content with increasing age. The average age for all the women was 40.7 ± 1.1 years. The average calcium content for the entire group was 10.858 ± 0.049 mg.

The usual statistical methods have been employed. For advice in connection with the use of these methods we are greatly indebted to Prof. J. Arthur Harris. A study of the relationship between calcium and age gave a correlation coefficient, $r_{A\text{Ca}}$ of -0.617 ± 0.035 for the women. (A = age in years; Ca = milligrams of calcium per 100 cc. of serum.) The coefficient is 17.6 times as large as its probable error.

The linear regression equation, calculated from the means, standard deviations, and correlation coefficient is $\text{Ca} = 12.007 -$

0.028 A, where, as above, Ca = milligrams of calcium per 100 cc. of serum, and A = the age in years. The empirical mean calcium contents as ordinates are plotted against the age in the chart. The empirical means are distributed with some irregularity around the lines given by the equations, but without large numbers of cases further tests of linearity seem unnecessary.



The results for men are given in Table II. There were 177 cases, ranging in age from 7 to 94 years.

TABLE II.—RELATIVELY NORMAL MEN.

Number of cases.	Age group.	Calcium in mg. per 100 cc. of serum.		
		Minimum.	Maximum.	Average.
22	7-17	10.0	13.5	11.6
42	18-28	10.0	13.5	11.4
24	29-39	10.0	11.0	10.5
22	40-50	9.5	11.5	10.4
23	51-61	9.5	12.5	10.3
27	62-72	9.5	12.0	10.2
14	73-83	9.0	11.0	10.0
3	84-94	9.5	10.5	10.0

The calcium content decreases with age. The average age for all the men was 42.3 ± 1.1 years. The average calcium content for the entire group was 10.746 ± 0.045 mg. A study of the relationship between calcium and age gave a correlation coefficient, $r_{A \text{ Ca}}$, of -0.594 ± 0.033 for the men. The coefficient is 18 times as large as its probable error.

The linear regression equation is $Ca = 11.772 - 0.024 A$. The empirical mean calcium contents as ordinates are plotted against the age in the chart.

Comparison of the two sexes shows that the age difference is only 1.6 ± 1.5 years, the average being 40.7 ± 1.1 for the women and 42.3 ± 1.1 years for the men. Thus the age groups are essentially comparable in years.

The difference in the average calcium content of men and women is 0.112 ± 0.066 mg. Since the difference is only 1.7 as large as its probable error, it cannot be asserted to be significant.

The difference in correlation in men and women is 0.023 ± 0.048 . Thus the correlations for the two sexes are in excellent agreement. This lends strong support to the conclusion of the existence of a material negative relationship between age and the calcium content of the serum.

Summary and Conclusions. 1. The average calcium content of the serum was found to be 10.858 ± 0.049 mg. in 141 women and 10.746 ± 0.045 mg. in 177 men. Thus, while the calcium content of the serum of women is 0.112 ± 0.066 mg. higher than that of men of comparable years, the difference may not be statistically significant.

2. The calcium content definitely decreases with age; in women it falls from an empirical average of 11.8 mg. at the age of 12 years to 9.7 mg. at the age of 78 years. In men it falls from 11.6 mg. at the age of 12 years to 10.0 mg. at the age of 78 years.

3. This decrease in calcium content can be quantitatively measured in terms of correlation. The correlation coefficient, $r_{A Ca}$, for women is -0.617 ± 0.035 ; for men it is -0.594 ± 0.033 .

4. If we accept the graduation of the means given by the straight-line regression equation the calcium content falls from 11.727 mg. at 10 years to 9.767 mg. at 80 years in women, and from 11.532 mg. at 10 years to 9.852 mg. at 80 years in men.

5. On the basis of the present data we conclude that there is no statistically significant difference in the mean calcium content or in the intensity of correlation of calcium content with age, in the two sexes.

NOTE.—We desire to express our gratitude to Profs. J. Arthur Harris and Clarence M. Jackson for valuable criticism in the preparation of the manuscript.

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MERCUROCHROME AS A BILIARY ANTISEPTIC, AS A MEANS TO VISUALIZE GALL BLADDERS, AND AS A POSSIBLE FORM OF TREATMENT IN CHOLECYSTITIS.

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ON account of the previous work of Hill and Scott¹ on the hepatic excretion of mercurochrome in rabbits, we were stimulated to undertake the present study. They demonstrated that mercurochrome is excreted in large amounts by the liver and, furthermore, that the drug may be present in the bile in bactericidal quantities. They were also able to prove that artificially produced infections of the gall bladder could be controlled by the intravenous injection of the dye.

Studies have been made by others, some of which agree with the findings of Hill and Scott and some of which are contradictory.

Hench, Snell and Greene, in 1924,² working with dogs, found that mercurochrome is concentrated and excreted by the liver without significant changes in the liver function, as determined by phenol-tetrachlorophthalein tests and by levulose tolerance tests. In a later paper,³ these authors confirmed their previous work in dogs, but found that, in these animals, bile, after the intravenous administration of mercurochrome, did not have the bactericidal action anticipated from *in vitro* tests. These authors believed that the bactericidal power of the drug was reduced by some conjugation or alteration during its excretion. Simmons⁴ found that mercurochrome (1 to 5000) in ox bile, killed typhoid bacilli in thirty minutes and (1 to 10,000) in one hour. The amount of culture and drug used in these tests was not given. However, he cites the work of Nichols, who failed to sterilize with intravenous injections of mercurochrome the bile of rabbits. These animals had previously received inoculations of 4 cc. of a heavy salt solution suspension of typhoid bacilli intravenously. He fails to consider that there is a possibility of other foci than the gall bladder. Simmons also cited Nichols' treatment of one human typhoid carrier with mercurochrome by mouth, for a week without benefit; a finding which we are able to confirm by further studies presented in this paper. Myer, Somer and Eddie⁵ were unable to obtain sterilization of rabbits immunized with standard typhoid vaccine and inoculated intravenously or intracystically with Eberthella typhi; although they found that the hepatic bile of rabbits which had received intravenous mercurochrome could destroy 10,000,000 typhoid bacilli in from six to twenty four hours. Zeligs⁶ has reported a case of acute typhoid cholecystitis in which the bile was sterilized by one intravenous injection of the drug; and Young,⁷ in his series of case reports includes one of a patient with biliary fistula in which the bile, after intravenous mercurochrome, contained the dye.

A. Oral Administration of Mercurochrome. The work was started both upon what were thought to be definite cases free from gall-bladder diseases and on cases about which there seemed to be no doubt as to the certainty of a cholecystitis. Seven of these cases had definite evidence of biliary disease. Four of them have subsequently been operated upon and a histopathologic diagnosis of cholecystitis has been made upon them. Three had stones. In 1 patient with arthritis a good result might possibly have been expected but was not obtained. In the other five it would be impossible to expect any therapeutic advantage from the dye.

(a) *Method.* Control duodenal drainages were done upon all cases prior to the administration of the dye. The position of the tube was fluoroscopically determined and the resultant flow was collected in a series of centrifuge tubes.

After thorough centrifugalization of a portion of the B bile which is supposedly from the gall bladder, 5 cc. of it was inoculated with a loopful of a virulent eighteen-hour broth culture of typhoid bacilli.

This was incubated twenty-four hours and two loopfuls were smeared upon Russel's agar. In all cases there was a luxuriant growth both of the typhoid bacilli and of contaminations present in the bile before inoculation.

The patients were then given salol coated tablets of mercurochrome varying from 200 to 500 mg. a day for a week. At the end of this time they were again drained and a repetition of the bacteriologic method listed above was carried out.

Chemical tests for the presence of mercury were also made on the successive specimens of bile.

(b) *Mercury Test.* 1. About 12 to 15 cc. of bile were mixed with an equal amount of concentrated hydrochloric acid and allowed to stand in the incubator overnight.

2. This was filtered into petri dishes and 5 to 7 small copper plates were scattered through the solution and allowed to stand overnight again at room temperature. (The copper plates had previously been thoroughly cleaned in concentrated nitric acid.)

3. The acid-bile mixture was decanted off the copper plates which were then thoroughly washed in tap water.

4. The plates were next heated over a Bunsén flame in a long pyrex test tube just comfortably wide enough to permit their insertion. Condensation was brought about by wrapping the portion of the tube near its mouth in wet filter paper or wet cloth. It was safest to heat until the plates were bronzed in appearance before they were dropped out.

5. A small crystal of iodine was dropped into the bottom of the tube after it had cooled off. If the iodine did not vaporize immediately gentle heat was applied.

When mercury was present the iodine united with it, with the formation of a brilliant red mercuric iodide just below that portion of the tube which was cooled during the original heating of the plates. The iodide usually appeared in long streaks. If large amounts of mercury were present a pretty web formation was seen.

As a control, we added 1 mg. of mercury in the form of mercurochrome to untreated bile. This gave a very definitely positive test.

(c) *Results of Oral Administration.* In 13 cases orally treated, we never saw a mercurochrome tint to the bile. Faint traces of mercury were found in 4 cases but never in sufficient concentration to have an inhibitory effect upon the growth of typhoid bacilli.

In this series of cases we were not able to see that the slightest improvement was obtained through this form of treatment.

So far as the routine urine tests might show there were no gross kidney changes. The van den Bergh reaction did not change one way or the other. As a matter of interest diastase tests⁸ were run upon the B fraction of each drainage. No significant change was found in the strength after the week of mercurochrome treatment.

Most of the patients became salivated at some time during treatment and two of these had considerable trouble and distress.

TABLE I.—DUODENAL DRAINAGE BEFORE AND AFTER ORAL ADMINISTRATION OF MERCUROCHROME.

Case.	Diagnosis.	Duodenal drainage before mercurochrome.					Duodenal drainage after oral administration of mercurochrome.					Remarks.			
		Dias- tase.	Types of bile.	As media for Typhosus B.	Urine albu- men.	van den Bergh.	Dias- tase.	Types of bile.	As media for Typhosus B.	Urine albu- men.	van den Bergh.		Mer- cury in 10 cc. bile.	Mg. mercury administered daily.	
1 .	Cholelithiasis	63	No "B"	Excellent	0	$\frac{1}{2}$ U. indirect	72	No "B"	Excellent	0	$\frac{1}{2}$ U. indirect	Trace	400 for 10 days	Salivation	Same.
2 .	Cholelithiasis	100	Normal	Excellent	Trace	0	88	Normal	Excellent	Trace	0	0	300 for 7 days	..	Worse.
3 .	Cholelithiasis	33	Normal	Excellent	Trace	1 U. indirect	27	Normal	Excellent	Trace	1 U. direct	0	500 for 5 days	Salivation	Same.
4 .	Cholecystitis	50	Light "B"	Excellent	Trace	1 $\frac{1}{2}$ U. indirect	48	Normal	Excellent	Trace	1 $\frac{1}{2}$ U. indirect	Trace	400 for 7 days	..	Same.
5 .	Chronic appendix Neurosis	53	Normal	Excellent	0	0	48	Normal	Excellent	0	0	Trace	200 for 7 days	Salivation	Same.
6 .		42	Normal	Excellent	0	0	46	Normal	Excellent	0	0	0	400 for 7 days	Salivation	Much better.
7 .	Cholelithiasis	86	Normal	Excellent	Trace	0	88	Normal	Excellent	Trace	0	0	400 for 7 days	..	Same.
8 .	Schizophrenia	46	Light "B"	Excellent	0	0	51	Normal	Excellent	0	0	0	400 for 7 days	..	Same.
9 .	Cholecystitis	92	Normal	Excellent	Trace	0	90	Normal	Excellent	0	0	0	600 for 7 days	Salivation	Same.
10 .	Cholecystitis	40	Normal	Excellent	0	0	20	Normal	Excellent	0	0	0	400 for 7 days	Salivation	Worse.
11 .	Neurosis	92	Normal	Excellent	0	0	102	Normal	Excellent	0	0	0	500 for 7 days	..	Same.

TABLE II.—SUMMARY OF EXPERIMENTS ON BILE AFTER INTRAVENOUS INJECTION OF MERCUROCHROME.

Case.	Diagnosis.	Treatment.			Laboratory findings.		Bacteriologic findings.	Remarks.
		Test No.	M-220 (cc.)	No. of spers	Notes.	Macroscopic appearance of bile.	Amount of mercury.	
12	No biliary disease	1	20	8	3 cc. $MgSO_4$ between (3) and (4)	Stained in (4) 23 min. after injection of dye	+(5-8)	1-hr. sterilization in (6); 24-hr. sterilization in (5-8).
14	No biliary disease	1	20	7	60 cc. $MgSO_4$	Fluorescence throughout, "B" particularly stained	Trace in (7)	24-hr. inhibition; 48-hr. sterilization in (7).
15	Chronic biliary, U.R.Q. adhesions	1	20	9	40 cc. $MgSO_4$	Fluorescence	+ to +	24-hr. sterilization in (5, 7); reduction to 2 colonies in (6).
16	Chronic arthritis	1	20	6	Fluorescence	0	Inhibition in (4-6)
17	Renal lithiasis	1	20	6	Much fluorescence and dye in (1-3), less in (4-6); tube slipped, bile diluted	+ + + in (1-3); + in (4-5)	24-hr. sterilization in (2) and reduction to 6 colonies in (3).
		2	20	6	0 to +	24-hr. sterilization in (5); colon bacillus persisting in the other tubes, no <i>E. typhi</i> .
18	Chronic biliary disease	1	20	8	Fluorescence, staining, decreased at the end	0 to +	24-hr. sterilization
		2	20	...	Drainage 24 hrs. after injection; not fasting	Very little dye	0	No inhibition
19	Cholecystitis	1	20	8	Very heavy dye	+ to +	24-hr. sterilization

Symptoms unchanged.
Copper plates in HCl in 5 days.

Much better.

No symptoms 4 months after second injection.
Much better.

	2	20	8	Drainage unsatisfactory; MgSO ₄ before and after tube in duodenum	Very little dye	0	No inhibition	No symptoms 6 mos. after second injection.
20 . . .	3	20	7	Inhibition in (1-3).	
	1	20	7	Very little dye	No inhibition	No improvement.
	2	20	6	Fairly heavy dye	+ to ++	24-hr. sterilization of <i>E. typhi</i> in (1-3); staph. present before inoculation persisting	No improvement.
21 . . .	1	12	9	Small amount of visible dye	Not done	No inhibition.	
22 . . .	1	20	6	No dye or fluorescence	0	No inhibition	
	2	20	5	++ in (6)	Inhibition in (1).	Much better.
23 . . .	1	20	7	Heavy stain (1-6)	24-hr. sterilization <i>E. typhi</i> in one specimen	Better?
24 . . .	1	20	7	Heavy stain (1-5)	24-hr. sterilization <i>E. typhi</i> in one specimen	Much better.
25 . . .	1	20	5	Heavy stain (3-5)	24-hr. reduction to 14 colonies in (5) and to 5 in (5).	
26 . . .	1	20	8	Drainage 18 hrs.	Heavy (2-4), little (1, 5)---See Table III.			
27 . . .	1	20	7		No inhibition.	
28 . . .	1	12	5	24-hr. sterilization of <i>E. typhi</i> in (3).	
29 . . .	1	20	6	++ (2); + (4); ++ (3, 5)	Sterilization of <i>E. typhi</i> but not of coccus in (1-4).	
32 . . .	1	12	5			

B. Intravenous Administration of Mercurochrome. The determination of the hepatic excretion of dye after intravenous injection in man was next attempted.

(a) *Method.* 1. Intubation of patient with duodenal tube,—position of bulb in duodenum was controlled by the fluoroscope as usual.

2. Intravenous injection of 20 cc. of 1-per cent mercurochrome.

3. Immediate stimulation of flow of bile by injection through the tube of 40 cc. of warmed 30-per cent magnesium sulphate.

4. Collection of resultant bile flow into sterile tubes. Capacity of tubes 20 cc.

5. Timing the appearance of first flow of bile and length of time through which it appeared.

6. Inoculation of bile specimens with typhoid bacilli or other organisms to determine germicidal or inhibitory qualities of mercurochromized bile. We used typhoid bacilli on account of their well known bilophilic qualities.

About 12 cc. of all the specimens were centrifugalized at a high speed for twenty to thirty minutes. One cubic centimeter from each tube was placed in a sterile Wassermann tube and inoculated with one large loopful of an eighteen-hour culture of typhoid bacilli. Immediately after the inoculation, 0.1 cc. of the organism-bile mixture was transferred to an agar slant to serve as a control for the number of organisms present at the beginning of the test. After twenty-four hours incubation at 37.5 C., another 0.1-cc. transfer was made in the same way, to determine the number of organisms left. In this way, it was possible to determine whether or not there had been sterilization or inhibition both of typhoid bacilli and of contaminations at times present in the bile before inoculation.

The bile remaining, after the withdrawal of the amounts desired for bacteriologic study, was mixed with equal amounts of concentrated hydrochloric acid and the test for mercury carried out as described above.

(b) *Immediate Effect of Intravenous Mercurochrome upon Bile.* Bile tinted with mercurochrome appeared in the siphoned bile between eighteen and twenty-three minutes after its intravenous injection. It continued to run in fairly high concentration for about fifty-five minutes. At the end of this time the tube was withdrawn. During the experiment, it was necessary to instil another 20 cc. of magnesium sulphate as the flow was becoming rather weak. Perhaps a third injection might have produced similar results.

About 15 to 20 cc. of the bile was collected into a series of tubes. Three of them were filled before the onset of the appearance of the dye and seven afterward. All were tested in the same manner for:

1. Bacterial qualities: The first three tubes showed no inhibition; tubes 4 to 10 showed varying amounts of inhibition to sterilization.

2. Chemical qualities: Tubes 1 to 3 showed no mercury; tubes 4 to 10 contained mercury in varying amounts.

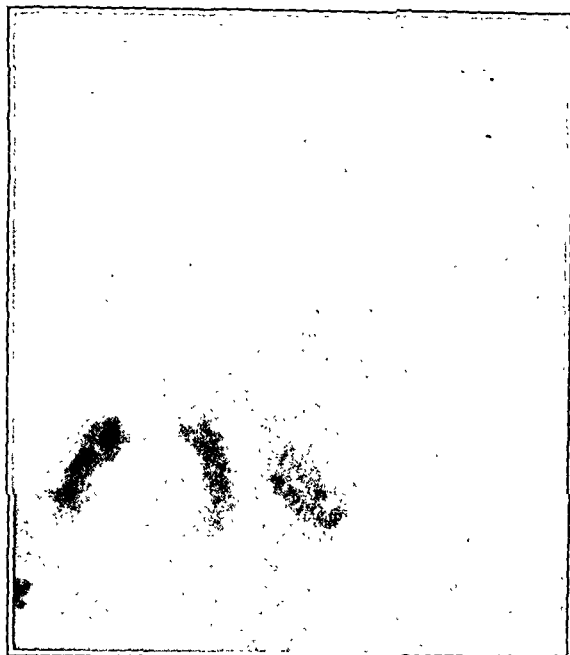


FIG. 1.—Gall bladder. Duodenal tube in stomach.



FIG. 2.—Gall bladder. Duodenal tube in duodenum.

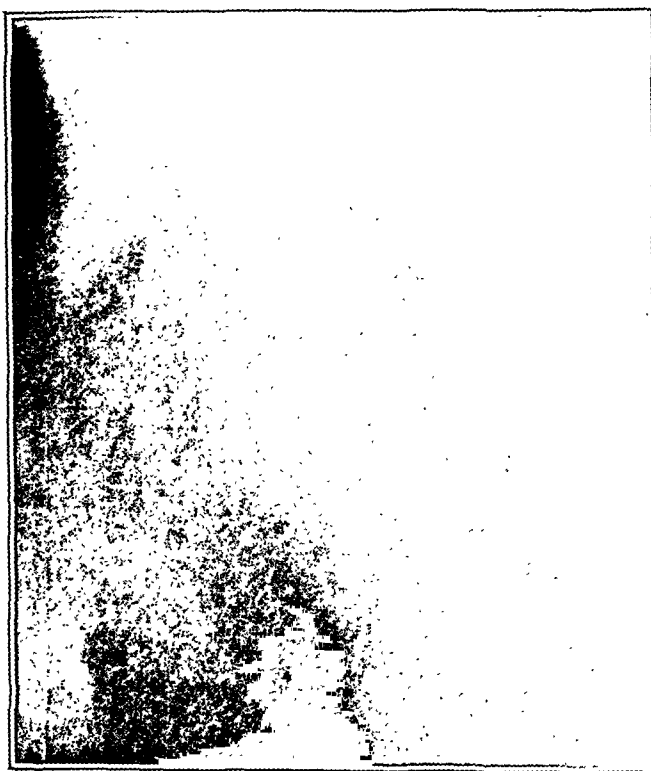


FIG. 3.—Gall bladder. Tube in pylorus.

(c) *Ability of the Gall Bladder to Store Mercurochromized Bile.* After the demonstration that bactericidal bile is excreted by the liver following the intravenous injection of mercurochrome, it became a matter of great interest to see if this type of bile could be stored in the gall bladder.

Method. Boyden⁹ and Whitaker¹⁰ have shown that the most complete emptying of the gall bladder may be obtained by the oral administration of egg yolk and cream. Consequently our patients were given the yolk of four eggs and a glass of half cream and half milk at noon. At 4.30 P.M. they were given varying amounts of mercurochrome by vein. Males usually received 20 cc. of a 1 per cent solution, females smaller amounts varying from 5 to 17 cc. After the milk-and-egg meal they fasted until the completion of the drainage. They reported to the dispensary the next morning when they were intubated with a duodenal tube (position controlled by fluoroscope). In the later experiments, it became routine to get Roentgen ray films of all the gall-bladder areas before and after the instillation of magnesium sulphate.

After siphonage was instituted, the bile was collected in a series of nonsterile centrifuge tubes; the contents of each tube was examined for its general appearance, that is, whether or not it contained visible amounts of the dye, its bactericidal qualities, and its mercury content. The tests described above were used for this purpose. Some of the more interesting findings will be recorded in detail.

Laboratory Results. A total of 25 complete examinations on 19 patients with 100 bile specimens have been collected and the end results are herein reported. Many other examinations have been attempted but for one reason or another have been incomplete. It has been of great interest to us to note the consistency with which siphoned bile contained considerable mercurochrome. At times the typical fluorescence was quite heavy. It was present in greatest concentration in the B bile which, as stated above, is supposed to come from the gall bladder itself and certain Roentgen ray evidence adds considerable weight to this theory.

In the 25 tests, a lack of inhibition was found only in 7 (28 per cent). In 4 tests (16 per cent) there was inhibition in some of the tubes. In 14 tests (56 per cent) there was sterilization; that is in 18 of the 25 tests (72 per cent) there was either sterilization or inhibition.

The mercury content has been measured by a qualitative method, but even so it is possible to gauge the amount into more or less rough groups which we have designated + to + + + +. In the majority of cases the amount of mercury has been proportional to the bactericidal or inhibitory strength of the specimen. At times small amounts of mercury have been found without any inhibition to bacterial growth. This was also seen in the cases which were treated with mercurochrome by the oral route. There was no inhibition without the presence of mercury. Details of 2 cases are presented.

Case Report. CASE I (No. 32).—Colored female.

Dosage, 17 cc. mercurochrome at 4.30 P.M.

Drainage, 11.30 A.M. next day. Five tubes collected.

Bacteriologic and chemical method as described above.

(a) SUMMARY OF RESULTS.

Tube.	Colonies before inoculation with <i>Eberthella typhi</i> .	Colonies 1 min. after inoculation with <i>Eberthella typhi</i> .	Colonies 24 hrs. after inoculation with <i>Eberthella typhi</i> .	Amount of mercury.
1 . . .	15 of Gram coccus	Massive growth of <i>E. typhi</i> , scant coccus	No <i>E. typhi</i> , 100 of Gram coccus	+
2 . . .	20 of Gram coccus	Massive growth of <i>E. typhi</i> , scant coccus	No <i>E. typhi</i> , 20 of Gram coccus	++
3 . . .	20 of Gram coccus	Massive growth of <i>E. typhi</i> , scant coccus	No <i>E. typhi</i> , 10 of Gram coccus	+++
4 . . .	55 of Gram coccus	Massive growth of <i>E. typhi</i> , scant coccus	No <i>E. typhi</i> , 30 of Gram coccus	+
5 . . .	20 of Gram coccus	Massive growth of <i>E. typhi</i> , scant coccus	Heavy growth of both organisms	+++

TABLE III.—BACTERICIDAL POWER OF DUODENAL FLUID FROM CASE II.

Tube.	Time.	Plate.	Control uninoculated.	<i>Eberthella typhi</i> .	<i>Eberthella dysenteriae</i> Flexner.	<i>Streptococcus pyogenes</i> .	<i>Staphylococcus aureus</i> 209.	Amount of mercury.
1 . . .	Start	A.	100 G. + c. and b.	Over 200	Infinite	Over 200	Infinite	++
	1 min.	B.	100 G. + c. and b.	65	Over 200	Over 200	100	
	24 hrs.	A.	Sterile	Sterile	Sterile	100	1	
2 . . .	Start	A.	50 G. + c. and b.	Infinite	Infinite	Over 200	Infinite	++
	1 min.	B.	50 G. + c. and b.	Over 200	Over 200	Over 200	Over 200	
	24 hrs.	A.	Sterile	Sterile	Sterile	Slight reduc.	Over 200	
3 . . .	Start	A.	Sterile	Infinite	Infinite	Over 200	Infinite	+++
	1 min.	B.	Over 200	Over 200	Over 200	Over 200	
	24 hrs.	A.	Sterile	Sterile	1	Over 200	
4 . . .	Start	A.	Sterile	Infinite	Infinite	Over 200	Infinite	+
	1 min.	A.	Over 200	Over 200	Over 200	Over 200	
	24 hrs.	B.	Over 200	Over 200	4	Slight reduc.	
5 . . .	Start	A.	Sterile	Infinite	Infinite	Over 200	Infinite	+
	1 min.	B.	Over 200	Over 200	Over 200	Over 200	
	24 hrs.	A.	Sterile	Infinite	20	Infinite	

This experiment is typical of a certain type encountered, in which the bile was germicidal for *Eberthella typhi*, but failed to kill the Gram-positive coccus. This organism, a yellow chromogen, which fermented dextrose and lactose but failed to liquefy gelatin, was frequently encountered in bile.

CASE II (No. 26).—White male.

Dosage, 20 cc. mercurochrome at 4.30 P.M.

Drainage, 10.30 A.M. next day. Eight tubes, of which Nos. 1, 2, 3, 4 and 8 were studied bacteriologically, as follows:

After centrifugalization four 1-cc. transfers of the supernatant fluid from each of the tubes studied were placed in small test tubes. One test tube

from each of the specimen tubes was inoculated with *Staphylococcus aureus* 209, one with *Eberthella typhi*, one with Flexner dysentery, and one with *Streptococcus pyogenes*. A large loop was used for these inoculations, which were made from eighteen-hour broth cultures—plain broth for all but the streptococcus which was transferred from blood broth. At once after inoculation 0.1 cc. was removed from each test tube and added to 9 cc. of melted, cooled agar. One cubic centimeter of this was transferred to 9 cc. of agar and both tubes were poured at once—plain agar being used except with the streptococcus for which blood agar was used. The results are summarized in the accompanying Table III. They show sterilization of *Eberthella typhi* by all specimens, and of *Eberthella dysenteriae* Flexner by four specimens. *Streptococcus pyogenes* showed no complete sterilization but a reduction from over 200 colonies to 1 colony in one, to 20 in another, and so forth. The poorest results were obtained against *Staphylococcus aureus*, three test tubes showing no effect on this organism, one a slight reduction, and one a reduction to 1 colony, therefore even here there was some evidence of inhibitory action on bacterial growth.

Roentgen Ray Evidence. After we had done several experiments, the thought occurred that the Roentgen ray demonstration of the dye in the gall bladder would be interesting. Consequently several patients have had films made and we have been fortunate in obtaining shadows of the vesicle in a few instances. The presence of gas in the hepatic flexure spoiled the picture in several cases. The reproductions of Roentgen ray films may be of interest:

Fig. 1 shows the gall bladder of a normal man. Fig. 2 shows one of a patient with migraine, Fig. 3 is of a neurotic colored man. In these cases, a normal filling and emptying was obtained by the Graham test which in 1 case was done four days before the injection of mercurochrome and afterward in 2 cases. We were not able to obtain gall-bladder shadows in the cases in which this tetraiodophenolphthalein test did not show gall-bladder concentration.

In this connection it is of great interest to note that eight vesicles which did not cast a shadow with tetraiodophenolphthalein were able to retain mercurochrome and evacuate it the next morning.

Immediate Clinical Results of Intravenous Medication. We always informed patients that they should expect a reaction and were rarely wrong. The reaction may be anything from a mild diarrhea or nausea to a marked chill with fever, vomiting and diarrhea. At times they feel quite "knocked out."

Urine tests were made in 12 of these cases and in 3 we found a transient albuminuria. Since so much of the dye is excreted by the liver and withdrawn through the duodenal tube it is rather difficult to imagine how any real kidney damage could be brought about. Dr. Young and his staff are quite certain that they have never produced any kidney lesion by its administration.

In 1 case there were streaks of blood with the bowel movements which were very frequent. This lasted for about eighteen hours.

Therapeutic Results of Intravenous Medication. In this small group of cases we are not prepared to draw any definite conclusions.

However, as we have injected eight individuals who have had evident signs and symptoms, coupled with laboratory findings, of cholecystitis, it may be of interest to produce our data.

We have treated these 8 patients; 3 of them have been unimproved, 5 have been markedly helped or are symptomless several months after the second or third injection. Of the 3 that were not benefited 2 were women and received small amounts.

TABLE IV.—RESULTS FROM EIGHT CASES OF CHOLECYSTITIS.

Case.	Sex.	Severity of symptoms.	No. of injections.	Amts. M-220 in cc.	Bacteriologic findings.	Mercury.	Results.
18	M.	++++	2	20 20	Sterilization No inhibition	+ to +++++	Remarkable improvement; returned to work after absence of 3 mos.
19	M.	+	3	20 20 20	Inhibition Sterilization No inhibition	Not done + to +++++ Not done	Greatly improved.
21	F.	++	1	12	No inhibition	Not done	No improvement.
22	M.	++	2	20 20	No inhibition Inhibition	0 + to ++	After severe gall-bladder colic, no symptoms.
23	M.	+++	3	20 20 20	Sterilization No drainage No drainage	Not done	2 injections gave symptomatic cure; recurrence after 6 mos.
32	F.	++	2	12 17	No drainage Sterilization	+ to +++++	Much better, no symptoms.
33	F.	++	2	5 12 12	No inhibition Sterilization of B. typhosus	+ Not done	No improvement.
34	M.	+	1	20	Sterilization	+ to +++++	No improvement

The frequent severity of the reaction is one of the commoner objections to the intravenous use of mercurochrome. As we have noted above, a reaction of some type is to be expected but never yet has a patient been unwilling to take a second or third injection.

Animal Experiments. To store mercurochrome in the gall bladders of dogs the same procedure was carried out as in human beings. They were given a fatty meal at noon, at 5.00 P.M. they received 8 cc. of 1-per cent mercurochrome by vein.

The next day at operation the contents of the gall bladder was withdrawn by syringe and bacteriologic and mercury tests similar to those done on human bile were carried out.

TABLE V.—DOG BILE.

Specimen taken from dog.	Colonies 1 min. after inoculation with <i>Eberthella typhi</i> .	Colonies 24 hrs. after inoculation with <i>Eberthella typhi</i> .	Amount of mercury.
20 hours after injection	Heavy growth of <i>E. typhi</i>	No <i>E. typhi</i> , 1 mold and moderate growth of Gram + b.	++
4 days after injection	Heavy growth of <i>typhi</i>	Heavy growth of <i>E. typhi</i>	0

Four days after the first operation the gall bladder was removed and the bile was again tested for its bactericidal property and mercury content. See Table V for results.

On another dog, the gall bladder was fixed in Zenker's solution after the mercurochromized bile was withdrawn. Microscopic sections were made, without staining the material, after a hematoxylin and eosin stain, and after washing the section in ammonium sulphide. In no instance were we able to demonstrate the presence of mercury or any damage in the cells of the mucous membrane of the organ.

Summary. 1. After oral administration of mercurochrome to the point of salivation in 13 individuals: (a) The bile was never bactericidal or inhibitory and never contained visible traces of the dye. (b) The treatment had no alleviating effects upon the symptoms of 8 individuals with cholecystitis.

2. Following intravenous injection of mercurochrome in man, the dye may be demonstrated in the bile siphoned out through a duodenal tube in eighteen to twenty-three minutes.

3. This bile is bactericidal and contains mercury.

4. Eighteen to twenty hours after intravenous injection, mercurochrome may be obtained by duodenal drainage. It apparently can be stored in the gall bladder.

5. This bile is bactericidal and contains mercury.

6. Eight individuals with cholecystitis have received mercurochrome intravenously. Three were not helped; five are clinically cured and their bile specimens were sterile.

7. The gall bladders of dogs contain mercurochrome eighteen hours after intravenous injection.

8. This bile contains mercury and is bactericidal.

9. Due to storage of mercurochrome in the gall bladder it is possible to obtain its shadow in Roengen-ray films.

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REVIEWS.

THE FUEL OF LIFE, EXPERIMENTAL STUDIES IN NORMAL AND DIABETIC ANIMALS. By JOHN JAMES RICKARD MACLEOD, M.B., LL.D., D.Sc., F.R.S., Professor of Physiology, University of Toronto, Canada. Pp. 147. Princeton, N. J.: Princeton University Press, 1928. Price, \$2.50.

THIS volume comprises four lectures delivered by the author at Princeton University under the Lewis Clark Vanuxem Foundation. This book, as the author states, deals especially with the question as to whether fat as well as protein forms carbohydrate before being used as fuel. He states that "According to our view neither protein nor fat is burned by the muscles until it has been converted into carbohydrate or some related substance, mainly by the liver." He then proceeds to give a fine compilation of the more recent evidence which has to do with this question.

Like any debated subject those who favor the view that carbohydrate can be formed from fat will feel convinced. On the other hand, those opposed will, most probably, not find enough to change their views. This book, however, should be of value to those interested, as it contains the current data bearing on this subject.

L. J.

THE PRESSURE PULSES IN THE CARDIOVASCULAR SYSTEM. By CARL J. WIGGERS, Professor of Physiology, Western Reserve University, Cleveland, Ohio. Pp. 200; 48 illustrations. New York: Longmans, Green & Co., 1928. Price, \$5.00.

THE author has produced an admirable monograph on this subject with which he has been himself so closely associated. The original work of Frank is well reviewed and a useful summary of Frank's equations for estimating and improving manometer efficiency is included. The whole subject is reviewed in detail from the point of view of establishing the facts without any long controversial discussion as to causes. There is little or no cause for criticism, though one may regret that Frank's equations for the optimum diameter of the tubing construction of a manometer is not included in the description of technical methods. It is an excellent book and should prove very useful.

H. B.

MEDICAL AND ALLIED TOPICS IN LATIN POETRY. By HEINRICH OPPENHEIMER, D. LIT., LL.D., PH.D. (LOND.), M.D. (HEIDELBERG), M.R.C.P. (LOND.), of the Middle Temple, Barrister-at-Law. Pp. 445. London: John Bale, Sons and Danielsson, Ltd., 1928. Price, 30 shillings.

A WAR-TIME enemy alien in England, the "innocent victim of social and—*horribile dictu*—to some extent of professional ostracism," the author sought comfort in the classical writers and soon found much medical material therein. This he has now presented, classified under some twenty-four such headings as Medical Sociology, Biology, Surgery, Insanity, Cosmetics, etc., the bulk of the text being quotations, interspersed with pithy, thumb-nail introductions two or three lines in length. A list of passages quoted, of translations, and a good index add to the usefulness of the book. Though the author denies any claim to have produced either a scientific work or a serious contribution to Roman medical history, others may fairly consider that he has done both. Fortunately, too, the author has included footnote translations of the Latin passages. In these non-classical days, a reversed position would have facilitated the progress of most readers. The alien is to be congratulated, also the publisher, who in happier times has brought out the alien's book.

E. K.

THE HARVEY LECTURES. DELIVERED UNDER THE AUSPICES OF THE HARVEY SOCIETY OF NEW YORK, 1927-1928. By DR. EDWARD FRANCIS, DR. FRANK C. MANN, DR. CARL F. CORI, DR. WALLACE O. FENN, DR. GEORGE R. MINOT, DR. E. S. LONDON, DR. THOMAS ADDIS, and DR. ALFRED E. COHN. Series XXIII. Pp. 280; 39 illustrations. Baltimore: The Williams & Wilkins Company, 1928. Price, \$4.00.

EIGHT discussions by the above noted distinguished physicians of these topics: Present Knowledge of Tularemia; The Relation of the Liver to Metabolism; Influence of Insulin and Epinephrine on Sugar in the Animal Body; Metabolism of Nerves; Treatment of Pernicious Anemia; Experimental Fistulæ of Bloodvessels; The Renal Lesion in Bright's Disease; Development of the Harveian Circulation.

R. K.

MALARIA PROBLEMS. By FREDERICK L. HOFFMAN, LL.D., Consulting Statistician, Prudential Insurance Company. Pp. 207. Privately printed, 1928.

THERE have been collected within one cover thirteen reprinted articles by the author, dealing with the public-health and economic

aspects of malaria, that have appeared in various journals since 1916, and a concluding 25-page statement of recent progress in malaria eradication in all parts of the world. The work serves well to visualize both the national and international phases of a problem that is of a particularly great importance in this country, its tropical possessions and its southern neighbors. R. K.

HORMONE UND INNERE SEKRETION. By DR. FRITZ LAQUER. Band XIX of "Wissenschaftliche Forschungsberichte." Pp. 136. Dresden and Leipzig: Theodor Steinkopff, 1928.

ONE of a series of "Reports on Scientific Researches:" surveys of the literature that has appeared in various scientific fields since 1914. In the present volume, No. XIX, dealing with hormones and internal secretion, the author has attempted a critical review based on over 1200 publications that have appeared from 1915 to 1927 inclusive, and he has succeeded remarkably well. R. K.

CHILD HEALTH AND CHARACTER. By ELIZABETH M. SLOAN CHESSEY, M.D. Pp. 204. New York: Oxford University Press, American Branch, 1927. Price, \$1.50.

ON the postulate that "as a knowledge of hygiene is the basis of health, so also in the study and application of psychology lies the great hope of increasing human happiness," "this little book has been written to help mothers to understand some of the health problems and psychologic problems from infancy to adolescence." The author has succeeded unusually well in presenting the psychologic material, especially in the chapters entitled, "The Toddler," "Child Psychology," "The Study of Character," "The Difficult Child," "Boys and Games," and "Adolescence." "Diet and the Health of the Child," "Sunlight and Health" and "Adolescence" are adequately presented, although the style begins to grow prolix, and the author at times inveighs a bit unduly against the carbohydrates: "very little wholemeal bread, no biscuits, cakes or rusks, nor rice or sago puddings." Hygienic principles and some rudimentary medical information are presented under "The Importance of Prevention of Illness," "Infectious Diseases in Childhood," "Sickness in the Nursery." Here again there is some unnecessary repetition, and, furthermore, the author has missed a golden opportunity to tell mothers something about prophylaxis against diphtheria, scarlet fever and smallpox: the Schick and Dick Tests, toxin-antitoxin and vaccination. The book can nevertheless be highly recommended to the lay reader. R. K.

PRESCRIBING OCCUPATIONAL THERAPY. By WILLIAM RUSH DUNTON, JR., B.S., A.M., M.D., Instructor in Psychiatry, Johns Hopkins University. Pp. 144. Springfield, Illinois and Baltimore, Maryland: Charles C. Thomas, 1928. Price, cloth, \$2.10; paper, \$1.35.

WHILE most physicians realize the importance of occupational therapy in one condition or another, it is safe to say that few of them have a clear understanding of the indications for and methods of applying this important branch of treatment. The subject receives no systematic presentation in medical curricula and the literature, chiefly a recent one, is largely restricted to special fields. This little book in Part I gives a concise statement of the general principles involved, and in Part II takes up the special application of occupational therapy to patients with mental disorders, general medical, surgical, orthopedic, cardiac, and tuberculous conditions, to children and to those who are bedfast. There are numerous references to collateral reading for those who desire more detail. The book should be particularly useful to the busy physician and the medical student. R. K.

NEW BOOKS.

*Recent Advances in Neurology.** By W. RUSSELL BRAIN, M.A., D.M. (OXON.), M.R.C.P. (LOND.). Pp. 412; 38 illustrations. Philadelphia: P. Blakiston's Son & Co., 1929. Price, \$3.50.

*Report of the International Conference on Cancer, London, July 17-20, 1928.** Pp. 588. New York: William Wood and Company, 1929. Price, \$12.00.

*You and the Doctor.** By JOHN B. HAWES, 2D, M.D. Pp. 181. Boston and New York: Houghton, Mifflin Company, 1929. Price, \$2.00.

Medical Clinics of North America. Southern Interurban Clinical Club Number, March 1929, Volume xii, No. 5. Pp. 306; 40 illustrations. Philadelphia: W. B. Saunders Company, 1929.

The Medical Department of the United States Army in the World War. Volume IV. Activities Concerning Mobilization Camps and Ports of Embarkation. Pp. 494. Washington: U. S. Government Printing Office, 1928.

*The Biochemistry of the Amino Acids.** By H. H. MITCHELL and T. S. HAMILTON. Pp. 619; 18 illustrations. New York: Chemical Catalog Company, 1929. Price, \$9.50.

* Reviews followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Clinical Significance of Cardiac Asthma: Review of 250 Cases.
—The syndrome of acute shortness of breath, paroxysmal in type, associated with a tendency to occur particularly at night, though sometimes following exercise, accompanied by a sense of suffocation, cough and sputum, has interested physiologists and cardiologists for a long time. The mechanism of production of this phenomenon, so satisfactorily relieved by morphin, has been a subject of discussion for some years, but no satisfactory evidence has been brought forth to explain completely the genesis of the symptom. PALMER and WHITE (*J. Am. Med. Assn.*, 1929, 92, 431), as the result of the study of a group of 250 patients, have this to say. A serious strain on the heart in all cases, involving chiefly the left ventricle and associated with other signs and symptoms of heart failure, especially the left ventricle, the attacks coming on when the patient is asleep in the recumbent position, lasting not more than half an hour, as a rule, associated with coughing up of blood and the prevention of the attacks by digitalization and rest are the high points which enable them to suggest that left ventricular strain and failure cause, with increased bloodflow, a stasis of blood in the pulmonary circulation, the right ventricle sending on too much blood for the left ventricle to take care of. Gradually this accumulation of blood in the pulmonary circuit increases, until by reflex stimulation the attack of asthmatic breathing is induced and the patient is awakened. By assuming the upright position the statis and strain on the left ventricle are reduced and recovery takes place. Morphin reduces the irritability of the respiratory centers, as well as other nerve centers, aiding the circulation by relieving the nervous strain. The authors summarize their analysis of the patients studied. The great majority were males and all but 14 were over forty years of age. The average duration of life was 1.4 years after the first attack of cardiac asthma, although the largest number of cases, 187, were found in patients with coronary disease, hypertension, or both, and the highest relative percentage occurred in syphilitic heart disease and in chronic nephritis.

The Relations of Syphilis and Diabetes to One Another.—The relationship between syphilis and diabetes mellitus has been a matter of discussion and controversy for nearly seventy years writes I. I. LEMANN (*Am. J. Syphilis*, 1929, 13, 70), who has reviewed the extensive literature on the subject from 1858 until the present time. The literature is gone over: (1) From the point of view of the cases of diabetes mellitus apparently due to syphilis; (2) the evidence for or against syphilis as an etiologic factor; (3) the rôle played by syphilis as a complication of diabetes; and, (4) the rôle played by diabetes as a complication of syphilis. Considering the very large number of patients who suffer from syphilis in this country and the very large number of diabetics, it might seem that there was some relationship between the two conditions, but that this evidence is most indefinite and the possibility is remote is shown by this study of the two diseases. There is not any conclusive and definite evidence that diabetes can be caused by cerebral syphilis. There is very little evidence and there are very few cases reported in which syphilis is the cause of true pancreatic diseases as proved at autopsy and only a comparatively few cases in which we may reasonably assume that diabetes might be due to syphilis. If, then, there is some connection between the two diseases, most assuredly the rôle of syphilis is a distinctly minor one in the genesis of diabetes. In an individual who has diabetes or in a person who has syphilis and becomes diabetic, the prognosis is increasingly grave except in the very occasional instances where the syphilis is responsible for the diabetes, under which circumstances the prognosis is better than in the non-syphilitic. Last, in his survey of the literature and from his personal experience, Lemann shows that a diabetic with a coexisting syphilis is probably more prone to artificial disease and more prone to gangrene, consequently, than is the diabetic without this complication.

Stereoscopic Radiograph of the Coronary System.—In a study of the minute anatomy of the vascular system there is much to present a clear picture of the genesis of many conditions which are the primary importance to the clinician. JOHN S. CAMPBELL (*Quart. J. Med.*, 1929, 86, 247) describes a method by which it is possible to make stereoscopic radiograms of the coronary system. The details of the technique need not be enumerated nor is it possible to discuss in detail the distribution of the coronary arteries. Suffice it to say that marked variations in the anatomic distributions of the coronary vessels are frequent and these are important in the clinical aspects of coronary disease. Anastomoses are peculiarly rich and are of great importance in preserving cardiac musculature, particularly in relation to coronary infarction. So rich is the anastomosis in many cases that coronary disease by this method of study has been found to be quite common without being suspected by the medical attendant. The heart is able to adapt itself to very marked alterations in the lumen of the vessels or the sources of its supply provided the lesion is not too sudden in onset or too extensive in degree. Incidentally, in relation to the clinical manifestations of coronary thrombosis and cardiac infarction, is the change produced by age in the coronary circulation. Marked tortuosity is apparent in the small vessels and the anastomoses seem to be considerably diminished on the right side, whereas on the left side there is an increase.

SURGERY

UNDER THE CHARGE OF

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Stricture of the Male Urethra.—CAMPBELL (*Ann. Surg.*, 1929, 89, 379) says that urethral stricture in the male is of prime importance among surgical lesions of the urinary tract. Over 90 per cent of urethral strictures are of inflammatory origin. Nearly all follow gonococcic urethritis. Since columnar and cylindrical epithelium favor gonococcus growth and squamous epithelium is resistant to this infection, inflammatory stricture is common to the anterior and bulbous urethra, but rarely found in the membranous portion. The latter, however, is the site of most traumatic strictures, the straddle injuries of the perineum. Improper treatment of the antecedent urethritis accounts for most gonorrheal strictures, even though the lesion may give no symptoms until twenty years later. Stricture depends on the severity of the urethritis, rather than on the duration. The majority of inflammatory strictures are clinically multiple, though pathologically they may be single. Traumatic strictures are usually single. The symptoms of stricture are varied, and may be present many years before acute local inflammation precipitates search of medical relief. Alteration in the size of the urinary stream, terminal dribbling, dysuria, frequency of urination, hematuria and an intermittent glut are perhaps most commonly observed. Urine shreds are always present with stricture. Urinalysis frequently discloses blood. Failure to respond to dilatation and certain complicating infections are the indications for operation. For deeper strictures perineal section must usually be performed. When this is done a perineal bladder tube should always be used. Preservation of free urinary drainage, free evacuation of the bowels and forced fluid intake sums up the immediate postoperative care. Numerous postoperative complications may develop, many of which are potentially fatal. The most important of these are urosepsis, hemorrhage and pneumonia.

The Treatment of Intestinal Obstruction.—ORR and HADEN (*Ann. Surg.*, 1929, 89, 354) state that, from the operative standpoint, obstruction of the small bowel may be divided into early and late simple obstruction and obstruction associated with circulatory disturbance or gangrene. In the early cases of simple obstruction immediate operation can be done with safety. In the late cases of simple obstruction operation should never be done without preliminary treatment of the dehydration and hypocloremia. In cases complicated by strangulation of the gut or gangrene early operation is imperative, but may with great benefit be preceded by salt-solution treatment. Dehydration and hypocloremia play major rôles in death due to intestinal obstruc-

tion. In every case sufficient salt solution should be given as rapidly as possible to correct these two conditions. Distilled water should never be used alone. Experimental evidence has shown it to be not only useless, but dangerous when introduced in large quantities under the skin or by enterostomy opening. Intravenous administration of glucose in 10 to 25 per cent solution is of great value in furnishing energy. It may be given with the salt solution. Enterostomy as a preliminary operative treatment is of undoubted value in selected cases. It should not be depended upon to the exclusion of water and salt. Treatment of intestinal obstruction with Welch bacillus anti-toxin or human bile by rectum requires further investigation to establish its value.

THERAPEUTICS

UNDER THE CHARGE OF

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The Treatment of Endocarditis Lenta by Cauterization at the "Site of Election."—Following up the original observations of Bier, CONSTANTIN V. BRAMANN (*Medizinische Klinik*, 1929, 25, 12), his assistant, reports upon the results of subcutaneous cauterization over the precordial area as observed in a group of 28 patients with endocarditis lenta. These patients are divided into two groups, an earlier one of 12 patients most of whom were in good general condition or still had mild grades of bacterial endocarditis, and a later group of 16 patients the majority of whom were in a very advanced stage. Of the first group 6 showed marked improvement, in only one of whom, however, was this improvement lasting. In the second group of 16 the majority died within three to six months after treatment. In 6 of them death was preceded, however, by a fairly prolonged period of improvement. Two patients with septic, malignant endocarditis, were apparently entirely cured by the treatment. The technique of the method consists in the creation of a subcutaneous pouch over the whole precordial area. A flatly curved incision is made through the skin and subcutaneous tissues over the upper portion of the chest under local anesthesia. Through this opening the tissues are elevated from the chest wall over a wide area and the entire inner surface of the pouch is carefully burned with a thermocautery, the margins of the incision alone being lightly burned. The flap is then sewed tightly into place. Marked pain is not produced as a sequel to this procedure. Elevation of temperature follows two or

three days after the operation but the fever usually subsides by about the eighth day. In some cases a secondary rise is observed. The operation is followed in many cases by marked increase in the appetite and in the ability to sleep, both of which often continue for several months. A small collection of fluid may accumulate in the sack but this is usually absorbed fairly readily. In the cases in which absorption is slow improvement seems to be more marked. Embolic phenomena disappeared for periods of months in 3 patients. Postmortem examination failed to reveal any direct influence upon the endocarditic lesion. The author believes that although the method cannot yet be regarded as promising a cure it is nevertheless of marked value by reason of its capacity to relieve symptoms, to improve health and to prolong life in these patients. It also seems probable that one of the patients is permanently cured although it is yet too soon to be certain. Repeated application of the treatment may give better results and the same may be expected when earlier cases are treated. All of those in these two series had been under intensive treatment by the usual medical methods and had failed to show any clinical improvement. The author suggests finally that the method may be a useful adjuvant to the usual medical methods of therapy.

**Experimental and Clinical Observations on Dodekamethylendigu-
guanidin (Synthalin B).**—In the course of their investigations on the action of guanidin derivatives NOTHMANN and WAGNER (*Klin. Wchn-schr.*, 1928, 7, 1996) observed that the toxic as well as the therapeutic actions of these preparations were diminished and delayed by the addition of methyl radicals. In the present communication, they report on a series of experiments with dodekamethylendigu-
guanidin which they have named synthalin B. Upon animals they find it distinctly slower than synthalin, dekamethylendigu-
guanidin, in its capacity to reduce the blood sugar. It is also materially less toxic although its toxic actions are qualitatively the same as those of synthalin. They have treated 150 diabetic patients with this new preparation and find, similarly, that its actions are the same in the human as those of synthalin differing only in intensity and rapidity of development. They recommend that the initial dose be 5 mg. three times a day and that this be raised within four or five days to a maximal dose of 15 mg. three times a day. They also recommend interruption of administration for one or two days after the drug has been administered daily for three or four days. These doses will care for from 30 to 50 gm. of sugar. The action is so slow, however, that a reduction in glycosuria often does not appear before the third day of the first course. The drug may be administered almost indefinitely upon the foregoing scheme. Its action in diminishing acidosis and acetonuria are similar to those of synthalin. Like synthalin, however, it is devoid of the trophic actions of insulin. Hence in greatly undernourished or in exceedingly enfeebled patients the strength and nutrition of the patient should be restored by the administration of insulin and synthalin B may then be used for continued treatment. While the several toxic actions of synthalin do appear with synthalin B the likelihood of their development is very much less and if they do develop they are of milder grade. No disturbance of liver function has been observed by the authors following its use.

PEDIATRICS

UNDER THE CHARGE OF

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The Monocyte in Active Tuberculosis.—BLACKFAN and DIAMOND (*Am. J. Dis. Child.*, 1929, 37, 233) found in their studies that 8 patients with steadily increasing monocyte-lymphocyte ratio died. In 3 patients, after an initial rise in the monocyte-lymphocyte ratio, the ratio was reversed and approached the normal ratio for the age. As the number of lymphocytes rose, it was noticed that the large young lymphocytes predominated. The changes in the blood preceded and pointed to the general improvement in the patients' condition. From their observations they feel that the degree of activity in tuberculosis is reflected in the peripheral blood of infants and children. A high ratio and the presence of epithelioid cells usually mean an active tuberculous infection. An increasing monocyte-lymphocyte ratio and the persistence of a high absolute monocyte count signify extension of the process. Reversal of the ratio or a fall in monocytes and an increase in lymphocytes denotes healing lesions. In cases in which the diagnosis is questionable a study of the blood by the supravital technique may lead to a correct diagnosis. After establishment of the diagnosis supravital studies of the blood may be of prognostic value in indicating whether the lesion is progressing or undergoing regression.

The Routine Use of the Vitamin B Factor in Infant Feeding.—DENNETT (*J. Am. Med. Assn.*, 1929, 92, 769) agrees with Macy and Hoobler, that cows' milk and sometimes breast milk does not contain the most satisfactory quantity of vitamin B; therefore some vitamin B besides that contained in cows' milk should be added as a routine procedure to the diet of all bottle-fed babies in much the same manner as cod-liver oil and orange juice are universally used. One-third ounces by weight or one level tablespoonful of wheat-germ sugar provides as much of the antineuritic factor as one quart of milk and as much of the antipellagic factor as ten ounces of milk. This sugar is most conveniently used, is more palatable and is more easily available than these. He feels that from one to three tablespoonfuls should be given daily to every bottle-fed infant throughout the first year of life.

Acid-base Metabolism.—SCHOENTHAL (*Am. J. Dis. Child.*, 1929, 37, 244) studied the effects of the administration of sodium chloride and of restriction of water on the total metabolism and the acid-base equilibrium of the body. He found that the administration of sodium chloride in infants in addition to a regular diet and in the absence of water restriction resulted in an increase in the chloride concentration of the plasma, a moderate reduction of plasma bicarbonate, a tendency of the plasma reaction to become acid, changes in the water content as evidenced by protein concentration, a constant increase in excretion

of bicarbonate in the urine with a shift in reaction toward alkalinity, a relative increase in excretion of fixed base over fixed acid, a decrease in György coefficient in the urine and usually a slight or moderate febrile reaction. The feeding of a concentrated food with the restriction of water produced the same changes in the metabolism as did the administration of sodium chloride. The blood concentration was marked and fever was high and symptoms characteristic of alimentary intoxication were observed. These results indicate the possible danger of the indiscriminate use of salt solution in children suffering from anhydremia. The effect of this administration may be to increase the degree of acidosis and to prevent restriction of a normal acid-base equilibrium.

The Physical and Mental Growth of Breast-fed and Artificially-fed Infants.—HOFER and HARDY (*J. Am. Med. Assn.*, 1929, 92, 615) analyzed the infant-feeding history of 383 elementary school children. They found that children who were artificially fed were, on the whole, physically and mentally inferior to the breast-fed. Except for height they ranked lowest in all the physical traits measured. From the standpoint of nutritional standards they were the poorest nourished group. They were the most susceptible to diseases of childhood. They were the slowest of all groups in learning to walk and talk. In mental development the artificially-fed ranked next to the lowest and the lowest were those breast-fed from ten to twenty months of age. Of the children with superior intelligence, the smallest percentage was found in the artificially-fed group, and not a child of this group was classified as being exceptionally bright. In considering the two types of artificial foods most commonly used in these children, modified cows' milk seemed to be a more satisfactory food from the standpoint of later development than unsweetened evaporated milk. The children who were breast-fed from four to nine months were definitely superior physically and mentally than all the other groups. Children who were fed exclusively on breast milk longer than nine months, although they seemed to develop at a normal rate physically, were the lowest group in mental development.

Observations on the Use of Irradiated Ergosterol in Active Rickets.—SOBEL and CLAMAN (*Arch. Pediat.*, 1929, 46, 1) administered ergosterol and found there was a decided improvement in the general well being, the appetite, the digestion, the color, the general behavior, the animation and muscle tone. Craniotables disappeared in two weeks and open anterior fontanelles diminished in size from four to two fingers in six weeks. The laboratory findings demonstrated a definite increase in the blood phosphorus to a normal level. Roentgenography showed a progressive calcification at the epiphyses and diminution of cupping and fraying. The irradiated ergosterol which was used was a 1 per cent solution of a commercial product not on the market. At first, large doses were used, but later relatively smaller doses were tried, and the results with these equalled those obtained with the larger doses. No untoward effects were noted either in large or small doses. They felt that the irradiated ergosterol is a powerful and reliable specific agent for active rickets, but as it is not biologically standardized it is safer to use smaller rather than larger doses. They feel that from the stand-

point of vitamin D it promises to supplant cod-liver oil and ultraviolet therapy, although cod-liver oil will still find its usefulness for its fat vitamin A content and ultraviolet therapy will be used for the general tonic effect and improvement of general metabolism. It was noted that in the fractures occurring in rachitic infants, callous formation and calcification were hastened by this therapy. It was used in a limited number of premature babies and also for the prevention of rickets in a small number of cases and the authors feel that it will replace cod-liver oil for these purposes. They feel that in the treatment of tetany, irradiated ergosterol will probably replace the use of calcium salts and parathyroid extract because of its greater ease of administration.

The Relation of the Altitude of the Sun to its Antirachitic Effect.—TISDALL and BROWN (*J. Am. Med. Assn.*, 1929, 92, 860) say that a marked increase occurs in the antirachitic effect of sunshine when the sun reaches an altitude of 35 degrees or more. A study of the geographic distribution of rickets shows that rickets is uncommon or exists chiefly in a mild form in those places where the minimum seasonal altitude of the sun is not below 35 degrees. On the other hand, severe rickets is met principally in those cities where the altitude of the sun is below 35 degrees for some months of the year. The period of the year during which rickets will probably develop can be calculated for any city. The duration of this period may be altered by prevention of exposure of patients to highly effective sunshine on account of unfavorable spring weather or other factors.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Absorption of Salicylic Acid by the Human Skin.—LESLIE-ROBERTS (*Brit. J. Dermat. and Syph.*, 1928, 40, 325) claims that absorption of drugs by the human skin has been demonstrated in the case of nicotin, aconite (Macht) and atropin. Friction brings about the absorption of mercury; but the number of other drugs actually absorbed without injury to the skin is small. In 62 cases studied by the author for absorption of pure synthetic salicylic acid through the skin, using a new colorimetric method, 48 showed the presence of the drug in the urine. Alcohol, water and vaseline were used as vehicles, and the concentration of the drug in the vehicle ranged from 3 to 50 per cent.

Definite evidence of absorption from areas as small as 1 to 2 square inches with a 50 per cent ointment were obtained. In two and a half hours 0.416 per cent salicylic acid was obtained in the urine from an area 4 by 5 inches. Alcohol favors penetration in proportion to its concentration. The absorption of the drug from aqueous solution reverses previous conclusions as to the absorption by the skin of drugs dissolved in this medium. The colloids of the connective tissue absorb the drug. Solid keratin, while impervious to salicylic acid, acts by an extraordinary adsorbing power, permitting a supersaturated solution to form on the skin surface. It is suggested that cholesterols are instrumental in the transposition of the drug.

Histochemical Studies on the Localization of Lipoids in the Skin.—ST. WAHL'S (*Arch. f. Dermat. u. Syph.*, 1928, 156, 303) studies indicate that lipoids are most abundant in the skin of the scalp and axillæ, and least abundant in the hairless regions. They are localized largely in the sebaceous glands and epidermis and least abundant in the sweat glands and hair shafts. The observations are of interest in view of Jaffé's theory that cholesterol and lipoids are necessary to the growth and nutrition of hair. The author's observations do not support the belief that the skins of patients with high cholesteremia have a high cutaneous cholesterol or lipid content.

Studies in Agglutinin Titer for Staphylococcus Through Specific and Nonspecific Vaccine Injection.—MICHAEL (*Arch. f. Derm. u. Syph.*, 1928, 156, 260) finds that normal blood serum agglutinates staphylococci in a concentration of 1 to 10 to 1 to 40. In furunculosis this concentration decreases to 1 to 1000 to 1 to 2000. The intracutaneous or intravenous injection of vaccine raises the titer to from 1 to 2000 to 1 to 10,000, whereas the subcutaneous injection of the vaccine raises it only to 1 to 400 to 1 to 800. The inflammatory reaction of the skin is believed to be responsible for the antibody formation. The effect is not specific, for similar methods of injection, using arthigon in gonorrheic patients, give rise to a similar increase in titer of serum agglutinins for staphylococci.

Does the Gennerich-Milian Reactivation of the Wassermann Reaction Exist?—BOAS and PORTMAN (*Arch. f. Derm. u. Syph.*, 1928, 156, 308) find that by running a series of controls which had not received a preliminary salvarsan injection, parallel to a series which did, no true provocative or activating effect could be demonstrated, the fluctuations in the series of tests (Kahn and Meinecke techniques included) being almost identical in both series.

Hypersensitiveness to Chinons.—MAYER (*Arch. f. Derm. u. Syph.*, 1928, 156, 331) believes he has traced the sensitization phenomena involved in fur dye and photographer's dermatitis to the chinon group in these compounds. Azo dyes are reduced by the living cell and thus act in cell respiration as oxidation equivalents. Aminophenol and phenylendiamin are intermediate stages in the formation of the chinons, which are the true offenders and act as the "antigens" in the cutaneous reactions.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Vaginal Hysterectomy.—Although there are many gynecologists in this country who frequently perform hysterectomy by the vaginal route, it must be admitted that by far the larger number of hysterectomies are performed through an abdominal incision. Those who routinely perform abdominal hysterectomy probably often wonder why the vaginal route would be selected by any surgeon as the method of choice. For the benefit of these men, let us review briefly the article by PETIT (*Am. J. Surg.*, 1928, 5, 252) of Paris, who reports a series of 123 consecutive vaginal hysterectomies with no mortality. He performs the operation under visual control without the use of clamps. The advantages which he claims for this method are that it produces a minimum of shock, reduces the danger of infection, simplifies the postoperative course, produces no abdominal scar, reduces the likelihood of the production of adhesions and reduces the time consumed by the operation. He believes that this type of operation is indicated in patients of advanced age or in a cachectic condition, especially in patients who have myomas of average size or total prolapsus after the menopause. The vaginal route is contraindicated, however, when the myoma is of excessive size or in cases in which myomectomy should be performed and also where there are extensive adhesions or coincident disease of the appendix.

Comparison of Salpingography with Tubal Insufflation.—The question has undoubtedly arisen in the minds of many conservative practitioners as to the relative merits and dangers of visualization of the Fallopian tubes by means of the Roentgen ray after the injection of iodized oil and the more simple peruterine tubal insufflation with carbon dioxide gas. Probably no gynecologist is more qualified to express an opinion on this subject than RUBIN (*Radiology*, 1928, 11, 115), who has been identified with this type of work for many years and for whom the latter test is named. He states that the chief value of lipiodol in gynecology is the aid it offers in radiographing the point of obstruction in the tube and of distinguishing submucous myomata of the uterus. Its disadvantages may be briefly stated. It remains for a long time in the sealed tube and in the peritoneum. In some cases he has found it in the tube over six months after its introduction. The patient should be warned of the presence of the lipiodol because it can cause confusion in case a ureteral stone is suspected. It may cause serious irritation and it

requires two workers, an expert roentgenologist and a gynecologist. It is not infallible, since when it fails to pass the tubes into the peritoneal cavity it does not necessarily indicate tubal impaction but this may be due to an insufficient amount having been injected for that particular case or spasm may intercept it at the uterine horn. When only the uterine cavity is outlined by the lipiodol it is impossible to say whether the tubes are obliterated throughout or only at the intramural portion. On the other hand, carbon dioxid insufflation demonstrates tubal patency as well as nonpatency. The gas is rapidly resorbed and leaves no trace in the peritoneal cavity. It is practically an innocuous procedure, simpler to perform and less troublesome to the patient than the lipiodol injection and can be repeated with greater safety. It is an office procedure without risk when carefully carried out, requiring but one operator. Its diagnostic value with respect to tubal closure is equal to lipiodol and the test can be repeated at stated intervals with the greatest simplicity. With increasing experience it enables one to diagnosticate the important points of obstruction in the tube lumen. It is superior to lipiodol in demonstrating tubal spasm, which can be graphically recorded by the kymograph. In doubtful cases and in those where operative relief of tubal obstruction is desired, hysterosalpingography may be resorted to. The contraindications are the same for both methods and in those selected cases where they are combined.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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(Concluded from April issue.)

"Aspiration" Experiments.—For many centuries the conception of Hippocrates—that aspiration of blood and mucus is the cause of pulmonary abscess—was accepted generally; and there seems to have been little or no doubt as to the aspiratory origin of postoperative abscess of lung in the minds of the older surgeons, who based their opinions largely on clinical observations. In view of this tradition, it is interesting to note that the early endeavors to create experimental pulmonary abscess by means of intratracheal inoculation were unsuccessful. (Aschner,²³ Lambert and Miller⁶ and Cutler and others.^{11,10,23})

Kline³⁹ was able to cause gangrene of the lungs of guinea pigs and rabbits by the intrabronchial instillation of fusospirochetal-containing material from a carious tooth. He interpreted his results as indicating that the aspiration of these bacteria from oral lesions of human beings may lead to a gangrenous process of the pulmonary tissue. Later, Kline⁴⁰ emphasized the importance of differentiating *gangrene* from *abscess*.

It remained for Smith¹⁹ to induce abscesses in the lungs of mice, guinea pigs and rabbits by the intratracheal injection of bloody material obtained from the teeth of patients suffering with moderately severe pyorrhea. Pointing out that lung abscesses in man commonly contain two or more of such bacterial types as spirochetes, fusiform bacilli, cocci or vibrios, Smith concluded that infected material from the mouth accounted for most instances of pulmonary abscess.

Interpreting the absence of postoperative lung abscess in 3500 tonsillectomies—performed under light ether anesthesia and with rigid precautions to prevent aspiration of blood and mucus—as an argument favoring the aspiratory route of infection, Crowe and Scarff,¹³ after repeated trials, succeeded in producing chronic lung abscesses in dogs by the introduction through a bronchoscope of a pledget of cotton saturated with fresh scrapings from human pyorrheal cavities. Analogous pulmonary lesions were obtained in two dogs following the placing of similar material in a frontal sinus. Inasmuch as the use of other bacteria failed to induce the same reaction, the authors suggest that the spirochetes in the pyorrheal lesions may have a specific rôle in the formation of abscesses of lung.

Simultaneously, Allen⁴¹ reported the reproduction of multiple abscesses in canine lungs following the instillation into the bronchi of warm pus from patients with chronic pulmonary abscesses. Moreover, the author learned that obstruction of a bronchus was an important factor in the causation of the abscesses.

Lately, Joannides,⁴² by introducing an admixture of fresh blood and human pulmonary abscess sputum into the bronchi of fourteen dogs, induced abscesses in ten of them. He considers as factors of great import in the production of pulmonary suppuration: (1) the abolition of the pharyngeal and cough reflexes in general anesthesia; (2) the presence of mucus or blood in the mouth during anesthesia; (3) the presence of "fuso-spirochætæ" in the buccal cavity; (4) the presence of chronic infection in the nose, mouth and paranasal sinuses; (5) the physical properties of the aspirated material; (6) the action of the cilia which clear the trachea and bronchi by rhythmic movement; (7) the specific immunity in the lung against certain bacteria, as for example staphylococci. Joannides agrees with Allen⁴¹ and Myerson^{43,44} that failure to expel aspirated material is more important than the aspiration itself and cites some recent investigations by Pilot,⁴⁵ who succeeded in producing abscesses in lungs of rabbits by intratracheal inoculation of fusospirochetal-laden material, which was caused to be retained there by the use of lipiodol.

Practically all of these experiments were performed on animals, anesthetized with ether. The influence of ether narcosis as a contributing factor to postoperative pulmonic infections is an old clinical observation and has been confirmed experimentally by Hoelscher,⁴⁶ who found previously-stained oral secretions, capable of producing pneumonitis, to be constantly present in the tracheobronchial tree of etherized animals. Corper⁴⁷ and his associates⁴⁸ observed that, under etherization, nasally-instilled fluids were inhaled readily by dogs and rabbits placed in a horizontal plane, whereas such aspiration did not occur in nonanesthetized animals. Furthermore, the recent experiments of Lemon⁴⁹ on etherized dogs showed that dyes, or barium suspension,

slowly administered orally, were drawn into the lower air passages except when the head of the animal was at least 28.75 cm. lower than the feet; and that, in accordance with Corper's⁴⁷ findings, aspiration could not be demonstrated in nonetherized dogs. Lemon concludes that "postoperative pulmonary infections may be explained, in part at least, as a result of infection carried to the lungs in oral secretion, which has been aspirated by the force of the air current when the chest expands, in patients whose protective mechanism has been disturbed"—a point also emphasized by Myerson,^{43,44} Allen,⁴¹ Joannides⁴² and Pilot.⁴⁵ These results are of interest when compared with those of Laughlen⁵⁰ who found a peculiar microscopic cellular reaction to intrabronchial droplets of liquid albolene in the lungs of infants dying of bronchopneumonia. The albolene had been placed into the nares as a routine procedure. In addition, Laughlen was able to reproduce a similar pathologic picture experimentally in animals. Instructive observations have been made on two occasions by Myerson,^{43,51} by Daily and Daily,⁵² and by Vail,⁵³ all of whom, by bronchoscopic examination of etherized persons immediately after tonsillectomy, found blood in the tracheobronchial tract in 79, 76, 78 and 62 per cent of their cases, respectively. On the other hand, Herb's¹⁴ study of the effects of anesthesia on the lungs led her to believe that under ordinary conditions properly administered ether is not any more likely to produce pulmonary complications than a local anesthetic.

Evidently believing that local anesthesia precludes or minimizes the possibility of aspiration, advocates of the "embolic" theory have pointed out that posttonsillectomic abscesses of lung have been reported in as high as 19.3 per cent of cases operated upon with the aid of a local anesthetic (Moore¹⁶); and that in some clinics (Gottstein,⁵⁴ Henle⁵⁵ and Mikulicz²²) more pulmonary complications occurred with local than with general anesthesia.

Contrariwise, Ochsner and Nesbit⁵⁶ have demonstrated that local anesthesia did interfere with the normal protective reflexes in over 600 cases of bronchography, done according to the "passive technic," and that aspiration did occur following the cocaineization of the pharynx. Surmising that the same condition might prevail in local anesthesia for tonsillectomy, they learned that in five individuals, so cocaineized locally, attempts to swallow iodized oil resulted in its entry into the trachea and bronchi instead of into the esophagus. The authors believe that their observations supply the missing link of evidence in support of the "aspiration" theory.

Interested in the same problem, Iglaue⁵⁷ noted blood in the larynx or upper trachea in 19 of 50 patients examined immediately after "local tonsillectomy." Inasmuch as in Ochsner and Nesbit's⁵⁶ series the patients had been instructed to swallow after being given the iodized oil, Iglaue observed the course of the lipiodol, slowly introduced into tonsillar fossæ after local tonsillectomy, without giving the 5 patients any instructions; and by fluoroscopic examination found some of the lipiodol in a bronchus in 2 cases, showing that "under ordinary tonsillectomy conditions blood enters the tracheobronchial tract in some, but not all, cases."

RETROSPECTOR'S NOTE.—From these observations it is clear that pulmonary abscesses have been produced in the experimental animal

following the introduction of infected material into the respiratory passages and into the venous circulation. Voluminous data have been presented in favor of, and contrary to, the tenets of both the "aspiration" and "embolic" theories. In the light of our present knowledge of the subject it would seem fair to assume that postoperative abscesses may result from infectious agents which arrive at the lung from the operative site by way of either the tracheobronchial, or the cardiovascular, route.

Irrespective of their controversial significance, these investigations have disclosed many factors, the avoidance of which should point the way to a reduction in the number of cases of postoperative abscess of lung: that is, improper anesthesia; failure to minimize or prevent aspiration of blood and mucus; pathologic processes which interfere with the physiologic mechanism of respiration and consequently favor retention of inspired infectious material; infection (especially fusospirillary-laden lesions) in the upper respiratory passages; infection in the operative field; undue operative trauma, and mass ligation of tissues.

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RADIOLOGY

UNDER THE CHARGE OF

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The Cancer Cell in the Practice of Medicine.—For many years MACCARTY (*Radiology*, 1928, 11, 379) has sought for earlier histopathologic evidence of malignancy than that commonly known. Often he has seen a suspicious condition, characterized by replacement of normal cells with undifferentiated cells, which has been designated secondary cytoplasmia. Since these cells were within the glandular acinus or tubule, a diagnosis of malignancy was not warranted, at that time. Nevertheless, MacCarty believes that all cell conditions which show an analogy to cancer should be radically attacked, for if one waits for the typical histologic criteria of cancer it will be too late.

Diverticula of the Stomach.—A case of diverticulum of the posterior wall of the stomach, near the cardia, is reported by KALBFLEISCH (*Am. J. Roent. and Rad. Ther.*, 1928, 20, 218). It produced no gastric or other clinical symptoms, and is therefore supposed to be congenital. The diagnosis was made by roentgen examination, alone. Due to the uncertainty of clinical symptoms, the preoperative diagnosis of diverticula of the stomach rests on the roentgen examination. Kalbfleisch lays stress on the roentgenoscopic examination in the upright and supine positions and especially in the oblique views. Decision as to treatment depends on the symptoms. No definite rules can be laid down. It should be kept in mind, however, that every diverticulum is potentially liable to the development of cancer.

In the same issue (p. 224) BERNSTEIN reports an instance of diverticulum on the lesser curvature one inch below the cardia. The patient, a woman, complained of attacks of pain in the lower right dorsal region accompanied by nausea and vomiting. The cholecystogram was normal and a barium meal revealed the pocket. Its appearance resembled that of perforated ulcer, and, as no mention is made of proof by operation, the reader cannot dismiss this possibility.

Radiologic Treatment of Carcinoma of the Cervix.—As a competitor of surgery, asks GELPI (*Radiology*, 1928, 11, 403) what has radiation to offer? He answers that radiation by deep therapy does not seem to be well adapted for the purpose and has not come into popular favor, but as an adjunct has a definite field of usefulness, particularly in the control of metastasis extending over large areas. Radiation with radium, however, is especially suitable for the treatment of cervical carcinoma, and the last few years have seen many converts from the ranks of surgeons. As to curability, Clark, of Philadelphia, one of the converts, has compiled statistics showing that radium gives a curability of 43 per cent as against 39.5 per cent by radical operation. The salvage, therefore, is practically equal, but the great difference lies in the primary mortality.

Ultraviolet Ray for Secondary Anemia.—At Iowa State College, JONGEWAARD (*Arch. Physiol. Therap., X-ray and Rad.*, 1928, 9, 504) has noted that about two-thirds of the girls coming to the clinic have secondary anemia, the hemoglobin ranging from 50 to 70. In all such cases the girls are urged to drink milk, eat largely of food containing iron, go to bed early and be out of doors as much as possible. When deemed necessary, treatment with the ultraviolet ray is given, beginning with an exposure of one minute and increasing until at the end of three or four weeks an exposure of fifteen minutes is applied to each side of the body. Patients thus treated have a marked increase of hemoglobin in from four to eight weeks. Although the work has not been extensive, Jongewaard believes that ultraviolet light may be given first place in the treatment of anemia, with food treatment a close second. A combination of the two seems ideal, since it is evident that sunshine is part of nature's mechanism for promoting the assimilation of iron.

Nonmalignant Tumors of the Duodenum.—GOLDEN (*Am. J. Roentgenol. and Rad. Therap.*, 1928, 20, 405) has found 17 instances of non-malignant tumors of the duodenum recorded in the literature and gives details of 2 cases personally observed. The ages of the 19 patients ranged from eleven days to seventy-five years. Most of the tumors were adenomas, a few were myomas, one was a hemangioma and one was a lymphangio-endothelioma. Symptoms suggestive of duodenal ulcer with hemorrhage were noted in many of the cases. In Golden's cases, as in several others, the Roentgen ray examination disclosed a rounded central filling defect in the duodenal bulb. Golden thinks that such a defect associated with a six-hour gastric retention may be considered as evidence of a growth arising in the stomach and prolapsing into the duodenum while the absence of such retention would point to a growth arising in the duodenum itself.

NEUROLOGY AND PSYCHIATRY

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Principles of a Rational Penal Code.—GLUECK (*Ment. Hyg.*, 1929, 13, 1) reviews the modern trend in investigation and reconstruction of the penal code with special attention to the recommendations of the Italian Penal Code Commission headed by Professor Enrico Ferri and the Fascist Penal Code prepared largely by Signor Rocco. From this consideration he organizes as the basic principle of legal procedure the following: "Society should utilize every scientific instrumentality for self-protection against destructive elements in its midst, with as little interference with the free life of its members as is consistent with such social self protection." Some such basic principle, he feels, is required in order to give coherence to the law because the older standards and principles on which laws are based are no longer pertinent to the situation. In modern society it is necessary to discard the old conception of punishment on the basis of just retribution or requittal of wickedness. He styles this principle as "sublimated social vengeance." Also the "expiative theory" must be discarded for the reason that expiation lies within the province of religion and not the province of criminal law. He agrees in principle with Dr. William A. White and Dr. M. Hamblin Smith that our attitude of hatred toward the criminal is a cultivated one in the nature of making the criminal a handy scape goat upon which one can transfer his feeling of his own tendency to sinfulness. He believes that utilitarian justifications of punishment are real and should not be lightly discarded in that the threat of arrest has a deterrent influence and the memory of past punishment has a preventive effect. These should be strengthened rather than weakened by rational modification of the penal code because under the existing system the criminal knows in advance the chances of probation and the length of imprisonment as related to contemplated crimes and he knows that at a certain time he will be given his freedom regardless of improvement or further deterioration. Therefore, the author proposes that we shift the emphasis from the isolated criminal act to the personality of the offender so that "for an offense relatively venial in itself, it is conceivable that a socially dangerous personality may remain incarcerated for life; and for one relatively serious it is likewise conceivable that a person who has profited by institutional or extramural treatment and gives reasonable scientific promise of permanent rehabilitation will be given his liberty after a comparatively short period. The vital element of the possibility of life-long incarceration if the individual is shown by scientific investigation to require it, may reasonably be expected to reinforce the natural deterrent effect of the threat of imprisonment."

Nevertheless, the author believes that punishment is only one of the devices that can be utilized in the correction of crime and that fear is not the only motive of conduct and probably not the most effective motive to appeal to in altering behavior. He calls attention to the trend toward individualization manifested in recent years by the classification of crimes into variations of degree and the "indeterminate sentence" movement, but considers these ineffective and inadequate. He criticizes with justice Ferri's recommendations for a schedule of "conditions of dangerousness" and "conditions of less dangerousness" in that the dangerousness of the criminal is but one feature of his personality make-up and that this principle does not recognize the social justice of constructive rehabilitative work on the basis of individual case study and need. From these considerations he draws his second principle, "The legal and institutional provisions for the protection of society must be based not so much upon the gravity of the particular act for which an offender happens to be tried as upon his personality—that is, upon his dangerousness, his mental and social history, his personal assets, and his responsiveness to penal correctional treatment." He considers that Ferri errs also in drawing up a minute schedule for the estimating of the degrees of dangerousness. He then sets forth four principles of procedure in sentencing criminals: "(1) The treatment (sentence imposing) feature of the procedure must be sharply differentiated from the guilt-finding phase. (2) The decision as to treatment must be made by a board or tribunal specially qualified in the interpretation and evaluation of psychiatric, psychologic, and sociologic data. (3) The treatment must be modifiable in the light of scientific reports of progress. (4) The rights of the individual must be safeguarded against possible arbitrariness or other unlawful action on the part of the treatment tribunal." For these purposes he would turn from criminal law to administrative law for the necessary machinery and considers that certain modifications in substantive law may be expected to result from this basic change in procedure, and these, together with the truly indeterminate sentence provision and improvements in penal correctional practice, would facilitate the work of the treatment body.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Speed of Appearance of Antibodies.—The general opinion has been that a considerable time elapses between the introduction of an antigen and the appearance of specific antibodies in the body fluids.

RAMON (*Compt. rend. Soc. de biol.*, 1928, 99, 1295) after subcutaneous injections of horses with filtrates of formolized cultures of *Bacillus pestis* was able to demonstrate in less than ten hours the presence in the blood serum of flocculating antibody. The author considers that this demonstration helps to explain the rapid "local immunity" obtained after the use of culture filtrates (Besredka).

Conjunctivitis of the Newborn.—The term ophthalmia neonatorum is so closely associated in our minds with the gonococcus that a report by THOMAS (*J. Infect. Dis.*, 1928, 43, 306) in which the causative agent in 100 cases was an atypical *Staphylococcus aureus* is of particular interest. The atypical characters were particularly the plemorphism of the cocci and the appearance of metachromasia with the smaller cocci staining Gram negative and the larger positive, seen in direct smear and in cultures, and in reactions with carbohydrates and pathogenicity for animals. *Staphylococci* identical to those recovered from the eyes were cultured from a large bottle of supposedly sterile olive oil used by the nurses to cleanse the skin of the infants and also from a dish of saturated boric acid solution used to bathe the breasts and nipples of the mothers before the infants were fed. It was, therefore, considered that the infection was probably thus transmitted.

Undulant Fever.—Ever since the close relationship between the human, *Bacillus melitensis* (Bruce, 1887), the bovine, *Bacillus abortus* (Bang, 1897) and the porcine variety has been recognized, the greatest interest has been aroused in human infections by any member of this group. It is of great importance from the epidemiologic point of view to have detailed information about patients with this infection many of whom have undoubtedly in the past been diagnosed as atypical typhoid fever, influenza or even tuberculosis or malaria or have remained undiagnosed. A recent report on undulant fever in New York State by GILBERT and COLEMAN (*J. Infect. Dis.*, 1928, 43, 273) brings most important evidence in support of the view that raw cow's milk is a frequent source of the infection in this country. The three types of bacteria are believed to be only varieties of the same microorganism which has become slightly modified by its more recent host and the disease produced should be diagnosed undulant fever. The above report is only one of a long list by American investigators and the European workers are of the same opinion so that it has been suggested by CERRUTI (*J. Trop. Med.*, 1927, 30, 230) that the name of the microorganism be *Brucella melitensis-abortus*, Bruce, 1887.

Intranuclear Inclusions in Yellow Fever.—TORRES and others (*Comp. rend. Soc. d. biol.*, 1928, 99, 1344, 1655, 1660, 1669, 1671) have issued a series of short notes upon some observations which they have made upon the tissues of monkeys infected with the virus of yellow fever obtained in Brazil. These authors describe acidophilic intranuclear inclusions arising in the liver cells of the infected animals. These inclusion bodies closely resemble those described by Goopasture and others, in herpes. The inclusion bodies consist of minute granular masses aggregated within the enlarged and ballooned nuclear membrane, within which the chromatin elements appear to have suffered dissolution. Their presence further supports the suggestion that yellow fever is a virus disease.

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AND

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DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE.
WASHINGTON, D. C.

Experimental Transmission of Yellow Fever to Laboratory Animals.—STOKES, BAUER and HUDSON (*Am. J. Trop. Med.*, 1928, 8, 103) report the results of experiments which they believe lead to the conclusion that yellow fever in West Africa has been successfully transmitted to monkeys of the species *Macacus rhesus*. Although the strain of the virus with which these experiments were carried out originated from a very mild and clinically almost undiagnosable case in an African, the following evidence supports the conclusion that this virus is that of yellow fever: (1) It was obtained from a case occurring during an epidemic. (2) It is transmissible from man to monkey, as well as from monkey to monkey by injection of blood or serum. (3) It is transmitted by mosquitoes of the species *Aedes aegypti*. (4) It is filtrable when in the circulating blood. (5) Convalescent serum from a severe case of yellow fever in doses of 0.1 cc. protects monkeys against infection with this virus, while 2 cc. of normal human serum fails to give any protection. (6) The clinical symptoms and the pathologic changes produced by this virus in rhesus monkeys are similar to those in human yellow fever. (7) At the close of the studies with this strain two additional strains of the virus were obtained, both from fatal cases of yellow fever in Europeans, in which the diagnosis was verified by post-mortem findings. Blood from each of these patients injected into rhesus monkeys produced fatal infections. From one of these two patients the disease was also transmitted to monkeys by means of mosquitoes. The clinical course of the disease and the lesions produced by these two strains were similar to those caused by the strain which originated from a mild case and with which most of the work was done.

Susceptibility of Eskimos to the Common Cold and a Study of their Natural Immunity to Diphtheria, Scarlet Fever and Bacterial Filtrates.—HEINBECKER and IRVINE-JONES (*J. Immunol.*, 1928, 15, 395) state that Eskimos are very susceptible to upper respiratory infections on contact with the outside world. Ordinary bacterial infections rarely occur. Diphtheria and scarlet fever are unknown clinically and in a group of about 50 subjects all were negative to the Dick test and all the adults were also Schick negative. Children up to the age of twelve years were invariably Schick positive. Three serums were found to contain anti-toxin both for diphtheria and scarlet fever. It is, therefore, concluded

that the immunity to the disease and the negative skin tests depend upon the presence of antitoxin. This is interpreted as being due to a natural hereditary immunity dependent upon some nonspecific antitoxic mechanism. Skin reactions with filtrates of streptococci isolated from cases of rheumatic fever were mildly positive in a small percentage of cases. Neutralizing antitoxin was demonstrated in all three sera, but it was not invariably present for all three toxins. The Eskimos showed a high percentage of positive reactions when tested with a *Staphylococcus aureus* filtrate.

PHYSIOLOGY

PROCEEDINGS OF

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SESSION OF MARCH, 1929

Hemoglobin Maintenance upon Synthetic Diets.—By D. L. DRABKIN and C. S. WAGGONER (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). Five dogs, fed upon the Karr-Cowgill diet¹ for periods of six to eighteen months maintained their hemoglobin at fairly constant normal levels. Sixteen grams (the quantity fed per kilogram body weight) of this synthetic ration were found to contain 0.052 mg. of copper. The copper was determined by the potassium ethyl xanthate method.² In the nutritional anemia experiments of Hart and his associates³ 35 cc. of milk consumed by a rat per day contained 0.01 mg. of copper. For a 50-gm. rat this represented 0.2 mg. copper per kilogram body weight. Therefore, in respect to the ingestion per kilogram of body weight, the amount of copper in the diet fed to our dogs was approximately one-fourth that supplied to Hart's rats on the whole milk (anemia-producing) ration. The hemoglobin maintenance levels of our dogs and the speed of recovery after single large bleedings were not influenced by the addition of CuSO_4 to the diet, raising the level of copper fed daily to 1.3 mg. per kilogram of body weight. The method of feeding the ration to which copper had been added was slightly modified to avoid the possibility of incompatibility between the CuSO_4 and KI in our salt ration (*i. e.*, formation of insoluble CuI). Furthermore, analysis of the excreta for copper indicated that most of the copper administered was retained by the animal.

It was of interest to determine the source of the copper in our original diet. Surprisingly, analysis of the individual salts in the "salt mixture" proved negative, while the copper content of the commercial casein (the protein component of the diet) and vitavose (used as the source of vitamin B) accounted for the total copper. Modifying the Karr-Cowgill diet by using coagulated egg albumin as the protein and Harris yeast concentrate and dry brewers' yeast as the sources of water-soluble vitamins and with other slight changes we constructed a "copper-free" synthetic diet suitable for rat-feeding experiments. By the addition of CuSO_4 to this diet, we had two similar synthetic rations complete in all known dietary essentials and different only in the presence of copper.

When fed *ad libidum* approximately 10 gm. of synthetic diet was consumed per rat per day. In several analyses of 10 to 20 gm. samples of diet by the xanthate method, which is sensitive to 0.01 mg., no copper was found in the ration designated as copper-free. The small quantity of copper added to the copper-free ration in making up the copper-containing diet was quantitatively checked by the xanthate method.

Most of the rats used were of a "skin-parasite-free" strain. They were kept in a special room in individual cages. The possibility of copper contamination of the rats upon the copper-free ration was eliminated. The animals were placed upon the special diets at the age of twenty to twenty-four days. The growth, general appearance and hemoglobin maintenance were normal in the rats on the copper-containing and also in those on the copper-free diet. Five rats upon a whole-milk diet developed a severe anemia. This anemia was promptly cured by placing these rats upon the copper-free synthetic ration. It should be mentioned that diarrhea invariably accompanied milk feeding and in two of the milk rats growth, which had been retarded, was promptly resumed on the copper-free diet.

Further experiments are in progress.

¹ Cowgill, G. R.: J. Biol. Chem., 1923, 56, 725.

² Scott, W. W.: Standard Methods of Chemical Analysis, New York, 1917, p. 165.

³ Hart, E. B., Steenbock, H., Elvehjem, C. A., and Waddell, J.: J. Biol. Chem., 1925, 65, 67. Hart, E. B., Elvehjem, C. A., Waddell, J., and Herrin, R. C.: J. Biol. Chem., 1927, 72, 299. Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A.: J. Biol. Chem., 1928, 77, 769, 777, 797.

The Relation of Climbing Fibers to Purkinje Cells in the Cerebellar Cortex.—W. H. F. ADDISON (from the Department of Anatomy, University of Pennsylvania). The nerve fibers entering the gray cortical substance of the cerebellum end as climbing terminals and mossy terminals. The former are associated with the Purkinje cells and the latter with the granule cells. Both were discovered by Ramon y Cajal; in birds in 1888, and in mammals in 1890. The classic type of arrangement of the climbing terminals, as shown by Cajal, is that of a single fiber lying along the Purkinje cell body and main dendrite, and branching at each subdivision of the dendritic arborization. In my study of young cerebella, prepared by the reduced silver methods, I have found many variations.

Frequently two and sometimes three climbing terminals are in relation with one Purkinje cell. These terminals approach the cell body from different directions, and therefore would not appear to be endings of one nerve fiber. Climbing fibers are seen to bifurcate, one branch becoming a climbing terminal, and the other branch continuing straight upward into the molecular layer between the Purkinje cells, quite independent of the latter. This latter variety of fiber terminates at the inner margin of the outer granule layer, sometimes in the form of a small enlargement or *bouton*. A variation of this arrangement is where a climbing terminal is given off from such a straight fiber, above the level of the Purkinje cell bodies, and then appears as a collateral of the straight fiber. Climbing fibers also subdivide in the inner granule layer and the branches diverge toward different Purkinje cells. The study of these young cerebella shows that (1) climbing fibers branch, (2) their branches probably terminate on different Purkinje cells, and

(3) Purkinje cells frequently receive terminals from more than one climbing fiber.

The fundamental nature of the process going on in the cerebellar cortex is associative, and it appears that the climbing fibers play an important part in this, along with the T-shaped axons of the granule cells, the short collaterals of the Purkinje cells, the much-branched axon of the Golgi cells of Type II and the basket terminals of the axons of the basket cells.

The Toxicity of Synthalin (Diguanidinodecamethylene).—W. G. KARR, W. BELK, and O. H. PETTY (from the Graduate School of Medicine, University of Pennsylvania). Synthalin was administered orally (in one animal, neosynthalin, subcutaneously) to dogs maintained on an ordinary house diet. It was given daily in amounts approximating the human therapeutic dose. After a period of two to five weeks the animals vomited, began to refuse their food, and died, with a marked loss of weight, two to three weeks later. The chemical analysis of the blood showed a progressive azotemic nephritis terminating with a marked nitrogen retention. There was only a mild albuminuria until the terminal stage and then accompanied by casts and red blood cells. During this latter stage an appreciable bilirubinemia occurred. Extended autopsy examinations were made and these showed, in particular, marked tubular degeneration of the kidney, especially of the small straight tubules occupying chiefly the deeper part of the cortex. The liver showed a diffuse fatty degeneration.

A Specific Conductivity Apparatus for Measuring the Conductivity of Serum Electrolytes.—F. W. SUNDERMAN (from the Department of Research Medicine, University of Pennsylvania). A specific conductivity bridge and a pipette cell adapted for measuring the conductivity of serum electrolytes agreed with the Kohlrausch method within ± 0.6 per cent in concentrations between 0.1 m. and 1 m. KCl. Somewhat greater deviations were found in more dilute and concentrated solutions. The bridge was constructed for us by the Leeds & Northrup Company and is a modification of the sugar-ash type of bridge.

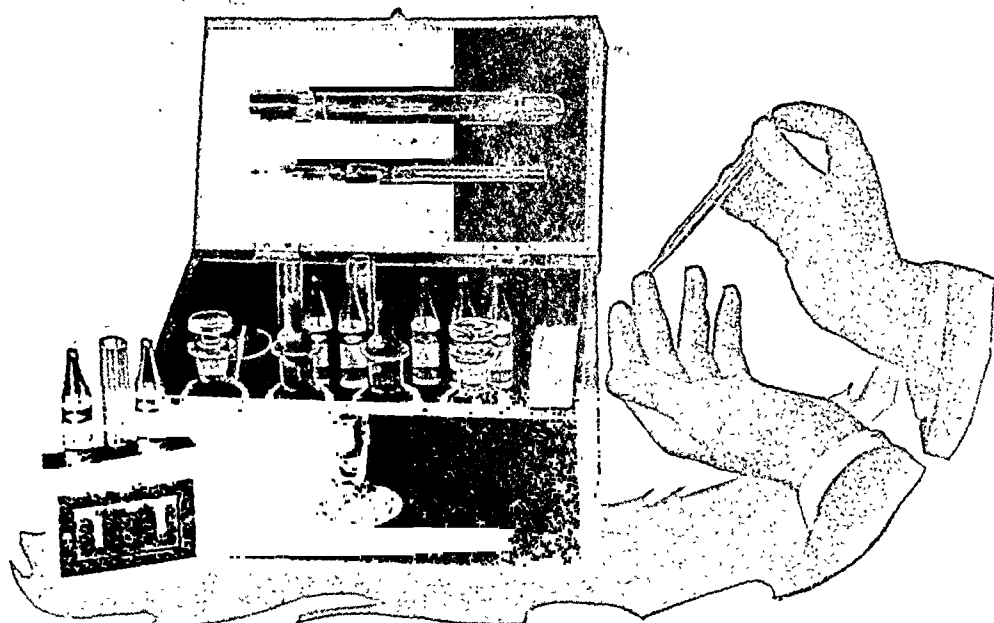
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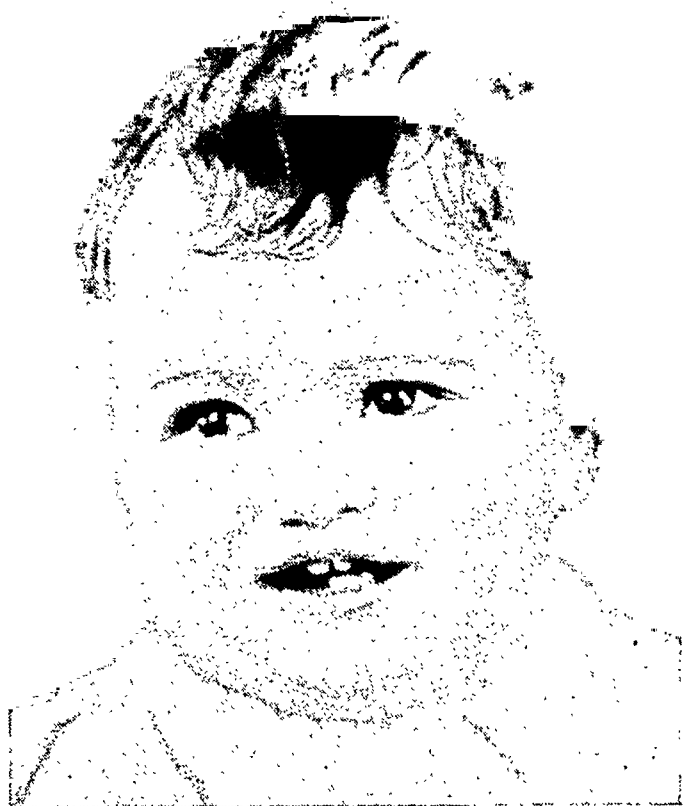
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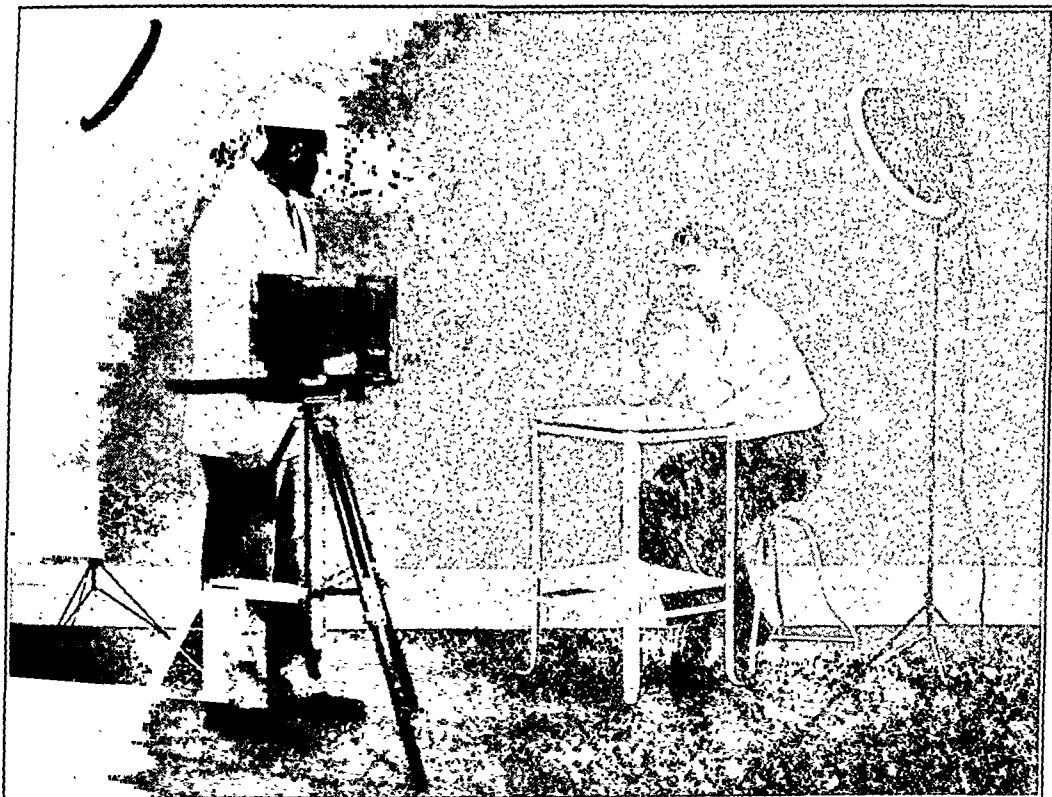
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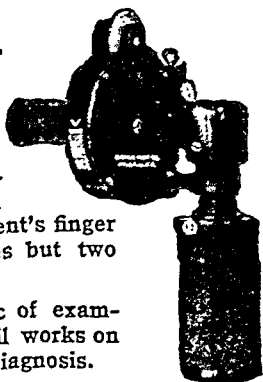
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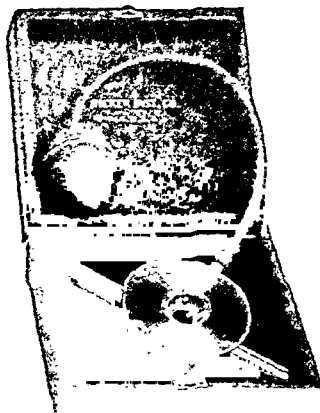
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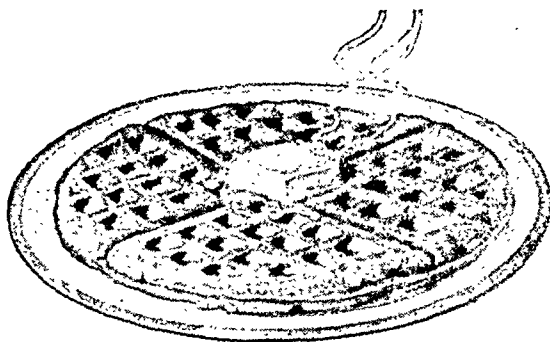
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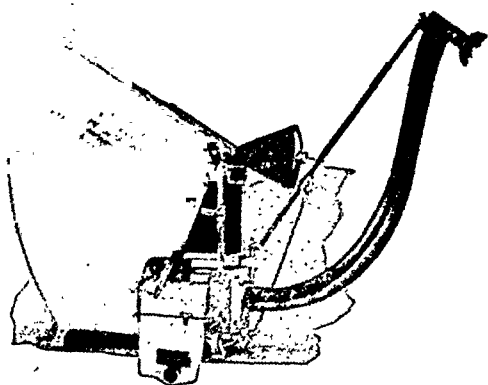
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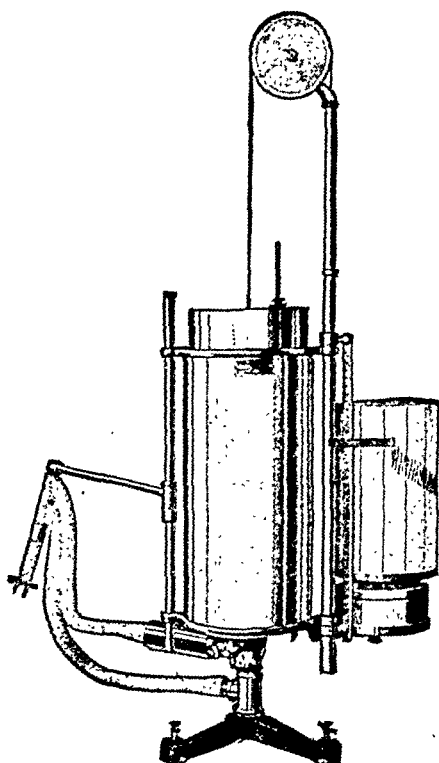
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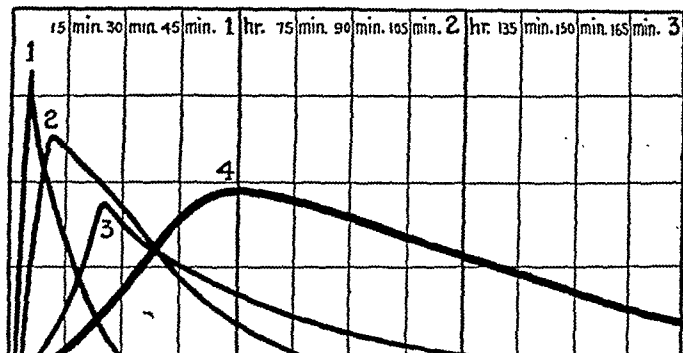
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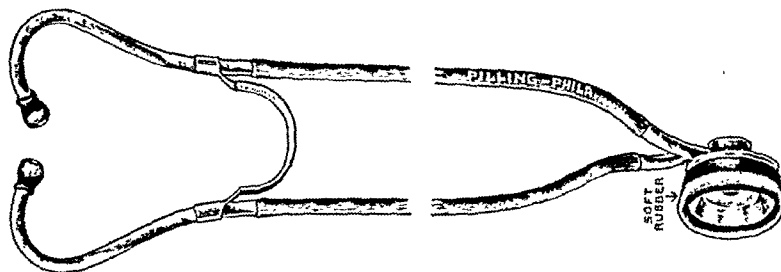


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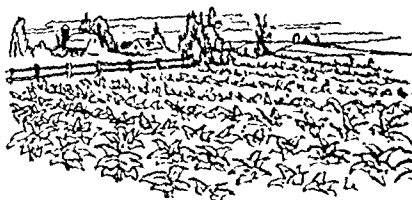
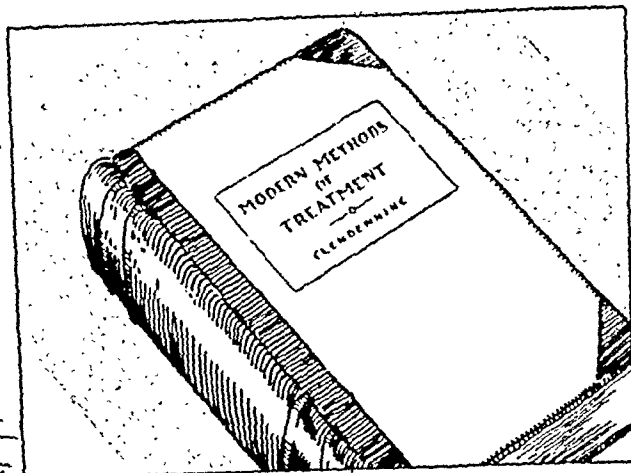
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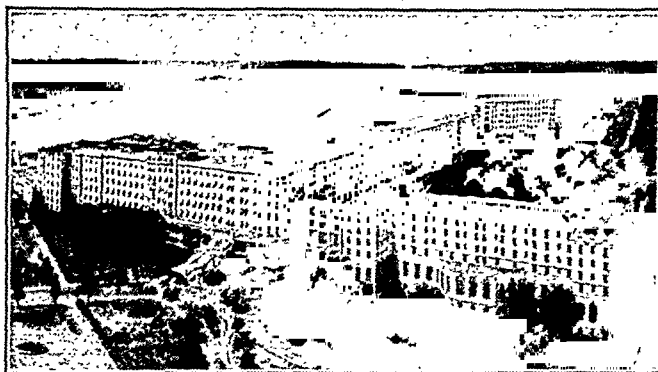
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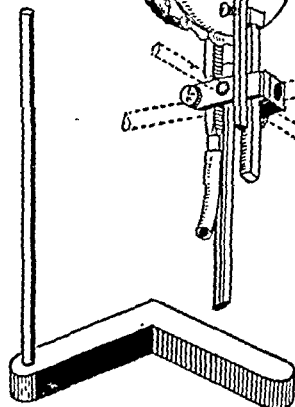
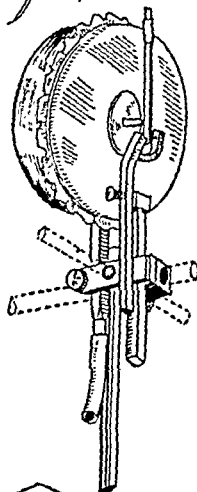
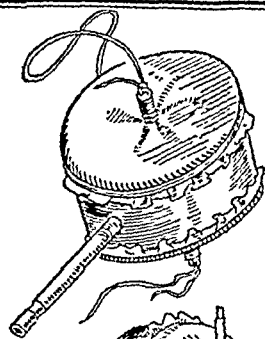
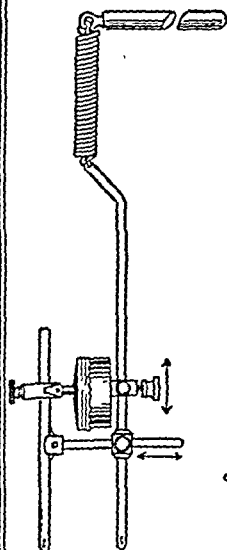
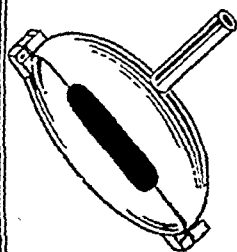
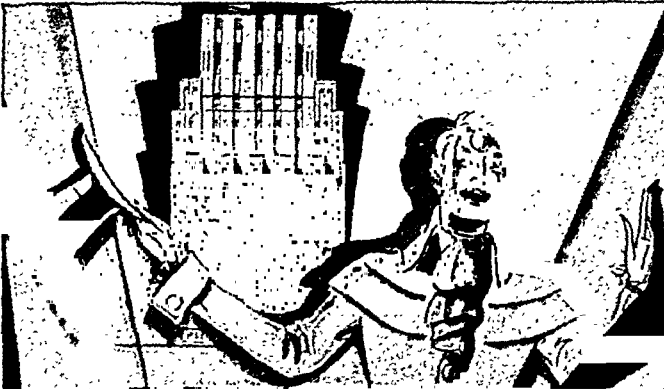
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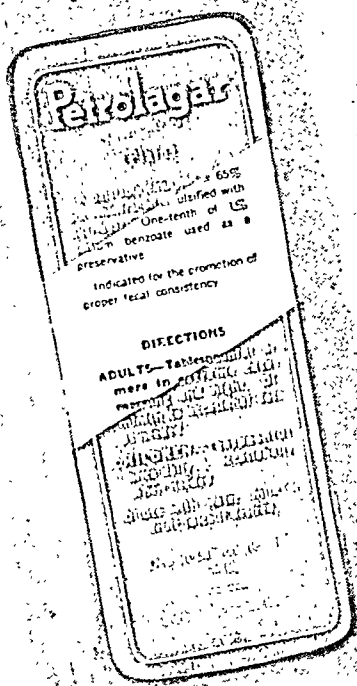
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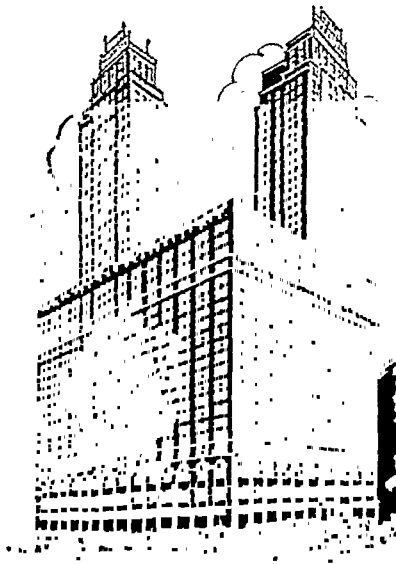
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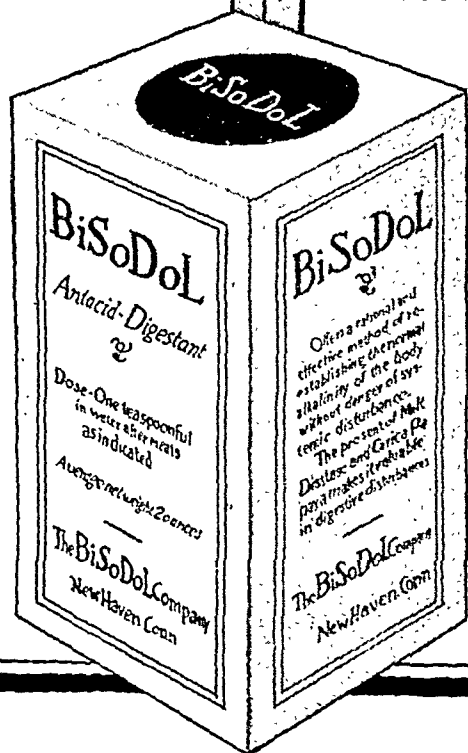
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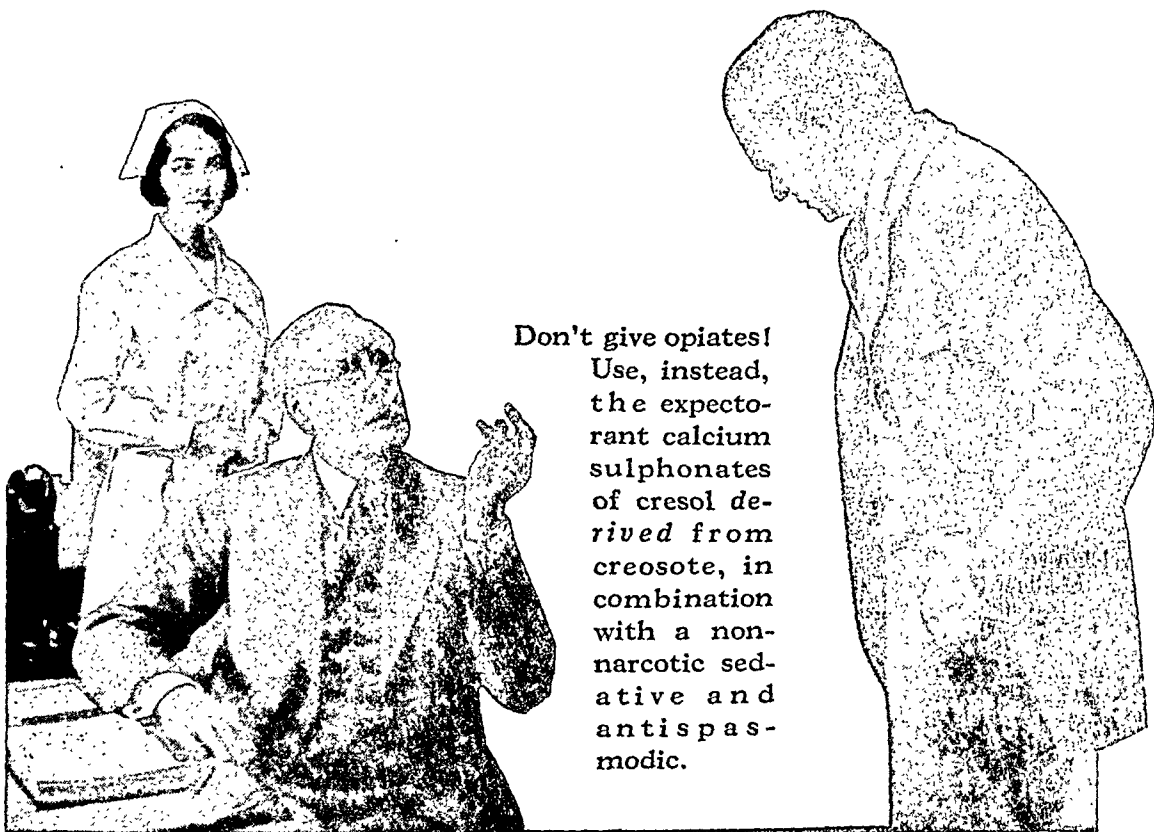
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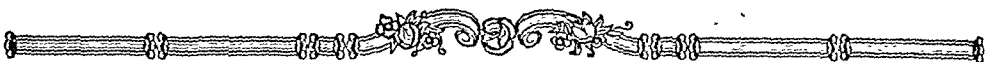
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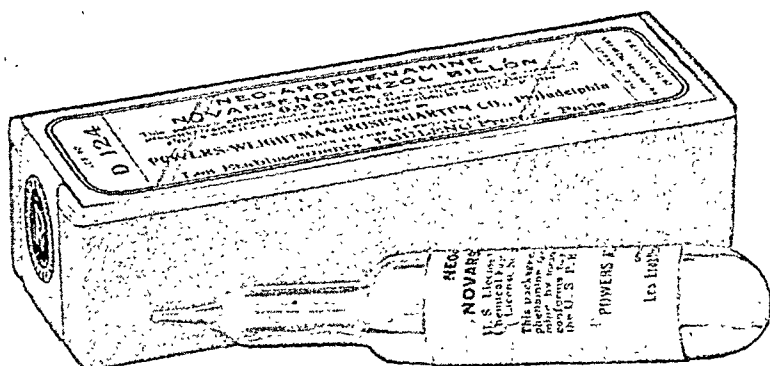
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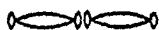
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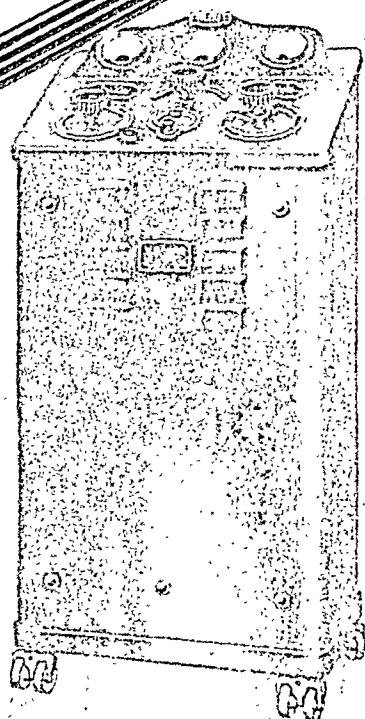
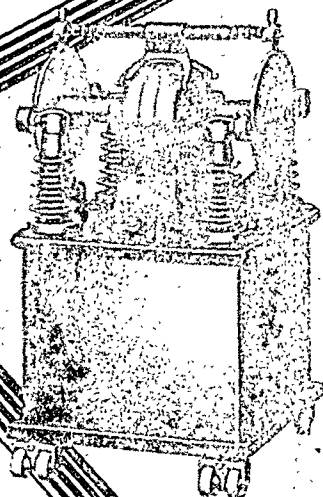
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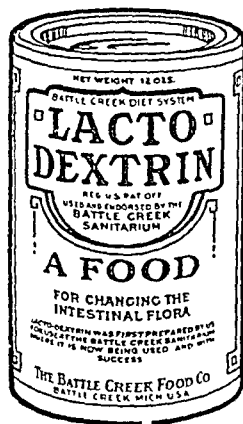
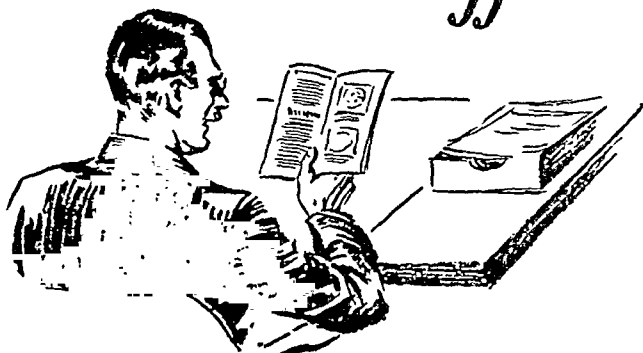
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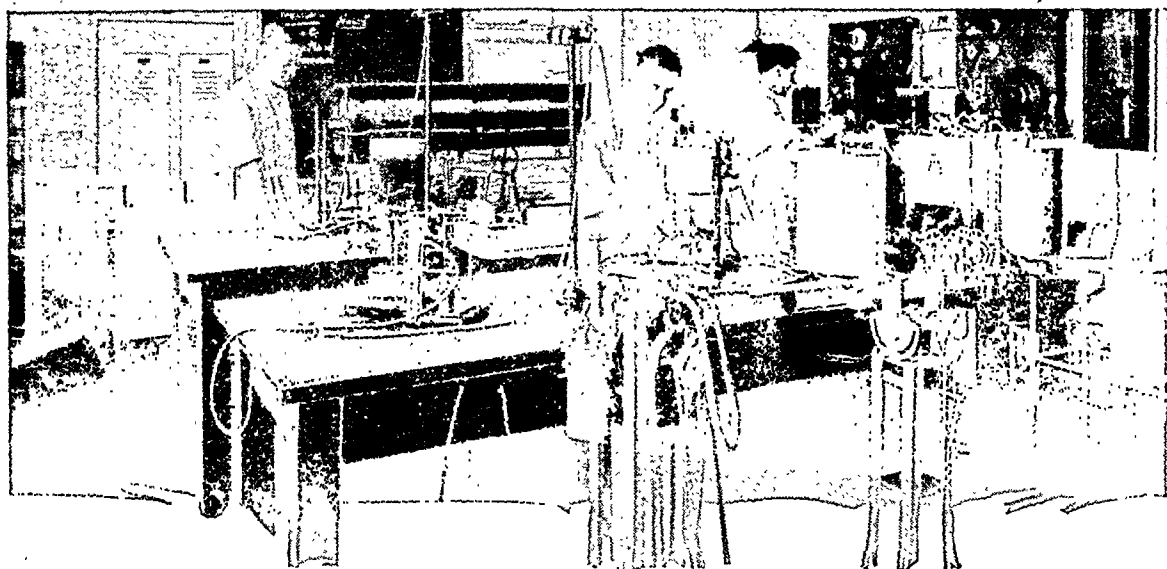
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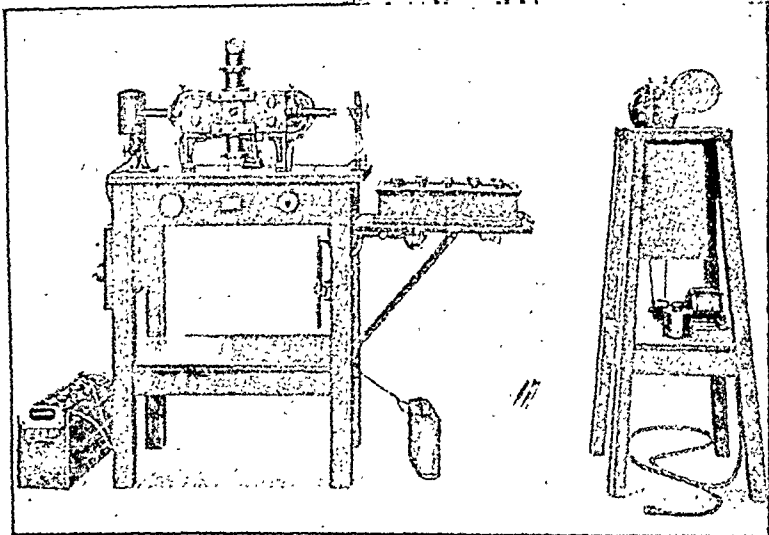
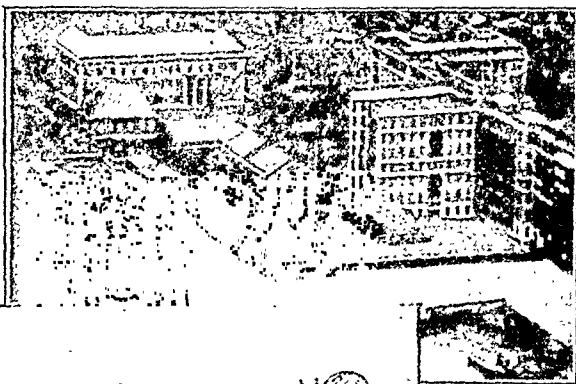
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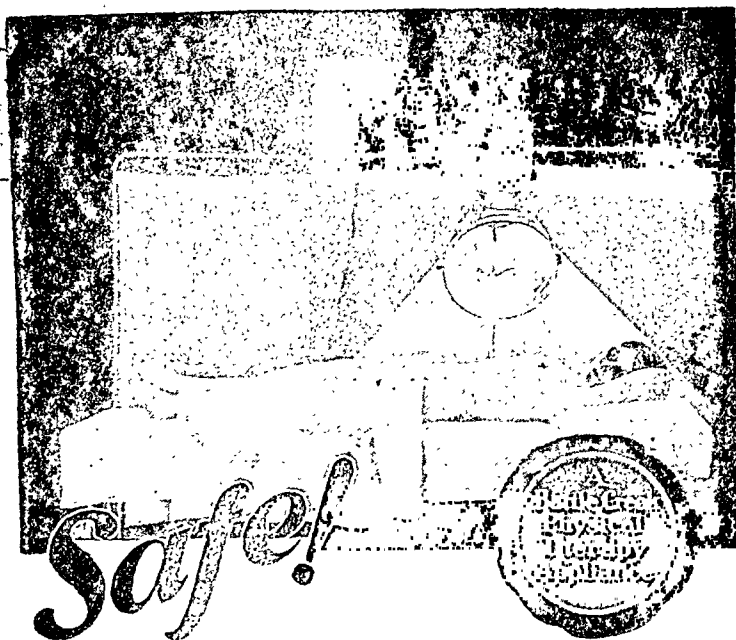
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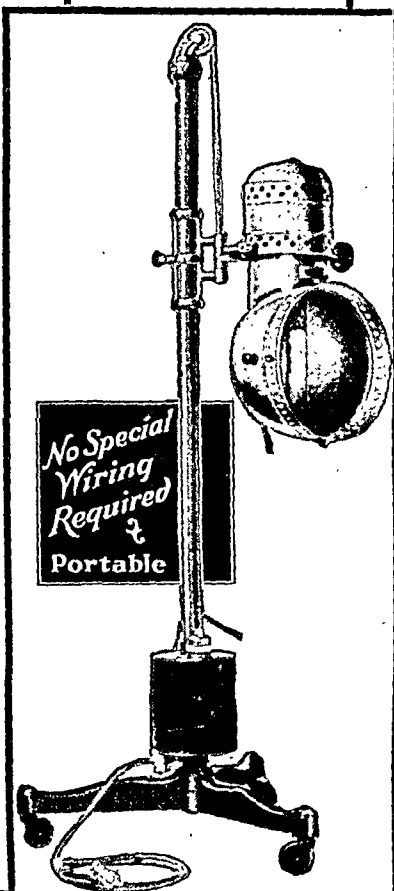
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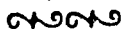


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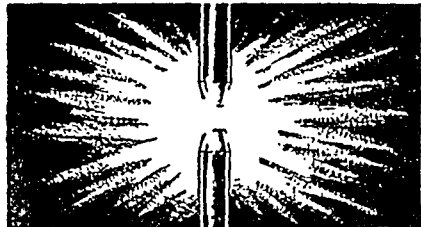
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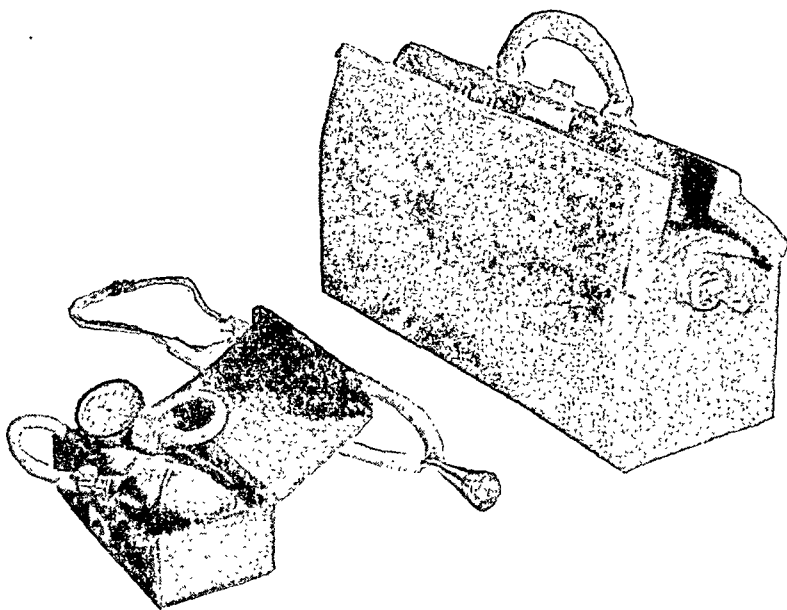
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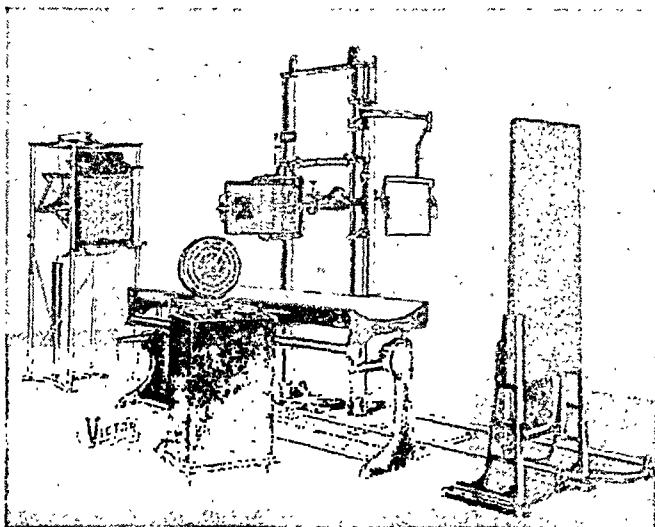
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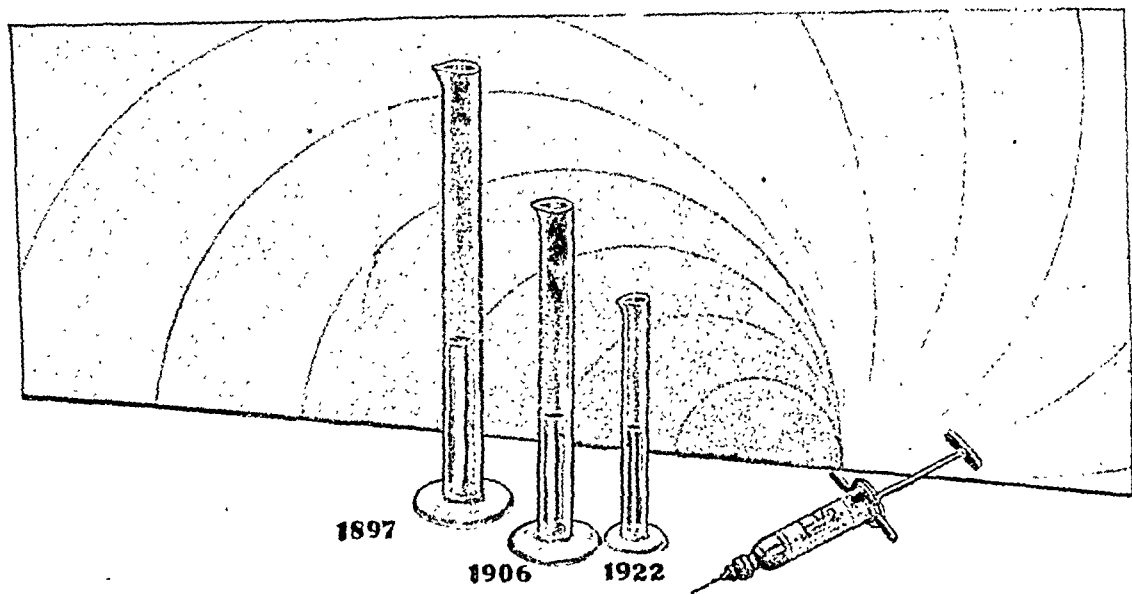
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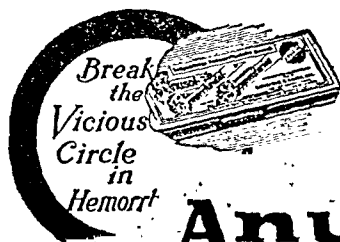
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THE
AMERICAN JOURNAL
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JUNE, 1929

ORIGINAL ARTICLES.

CHRONIC APPENDICITIS.*

BY JOHN B. DEAVER, M.D.,

SURGEON IN CHIEF, LANKENAU HOSPITAL, PHILADELPHIA, PA.

My reason for speaking upon chronic appendicitis is because of what I believe to be unwarranted statements that chronic appendicitis is not a clinical entity, statements that are being made by those whose observations on the living subject at operation are not sufficiently large to warrant such pronouncements. I hope to show the fallacies of these statements. There is no doubt but that many deaths result from an acute exacerbation supervening upon a chronically diseased appendix, which naturally is more vulnerable than the normal appendix, so that loss of life may often be the price the patient pays for this erroneous attitude.

At the outset, it must be admitted that the first and most important step in the handling of any morbid condition is the diagnosis. Diagnosticians of today are of three classes, the clinician, the radiologic-clinician and the radiologist. The first acquires experience and judgment by time and labor spent in the study of pathology and from a large practice in which he has seen and treated all types of disease. This fortunate doctor is of much value to his clientele, especially if he has been tutored by a Master, and has the prerequisites of good common sense and the ability to use the special senses with which nature has endowed him.

The radiologic-clinician is he who depends as much, if not more, upon the radiologic than upon the clinical findings, with a consequent weakening of his own confidence. I feel it is because of this that the average medical man or the average surgeon of today is not as

* Read before the Inter-State Post-Graduate Association of North America, Atlanta, Ga., October 15, 1928.

good a diagnostician as in former times. Too many doctors are unwilling to venture an opinion in the chronic abdominal case without a roentgenogram. In fact, the laity now know so much, or rather so little, about the picture business that they demand this form of examination. My answer to this request is, "I am not yet a picture doctor." The radiologist is the third type of diagnostician who studies the case from its roentgenologic manifestations but familiarizes himself with the history of the case before he gives his report.

However this may be, there are certain points that every diagnostician must bear in mind. The appendix is a diverticulum, an offshoot of the alimentary canal, with a like anatomy, histology and physiology, and with a vascular supply out of proportion to its size. The mucous membrane is ciliated with the cilia directed toward the outlet and the arrangement of the muscular coat such as to favor contraction in the same direction. This arrangement of the anatomy enables the appendix to empty when its lumen does not contain foreign matter, such as fecal concretions, and when the coats are infiltrated by products of inflammation. The valve of Gerlach at its outlet prevents regurgitation of the cecal contents only under normal conditions. Unsuccessful efforts of the appendix to empty cause appendiceal colic, therefore, as appendicitis is primarily the result of disturbed anatomy which necessarily affects the physiology. The physiology of the appendix was carefully considered and proven long ago by the famous Scotch surgeon, Sir William MacEwen whose deductions were always logical. MacEwen reached his conclusion by a study of the cecal secretions obtained through a fistulous opening in the cecum close to the appendiceal opening, and concluded that the appendix plays a part in cecal digestion and that the cecum and the appendix play an important part in the final stages of intestinal digestion. Practically, therefore, the physiology of the appendix plays a rôle in the pathology of inflammation of the appendix. Furthermore, recent studies show that a connection exists between the appendix and the ileocecal muscle, demonstrable by electric stimulation; also that the appendix is part of the cecal apparatus, that is to say, a lymphatic portion of the intestine with an accessory digestive action, and finally, the mutual influence of the lymph follicles of the gastrointestinal tract, as evidenced by its action in producing changes in the ingesta, seems to regulate intestinal activity in general just as the appendix does in its own region. One of the functions of lymph follicles, as we all know, is to prevent inflammation. Thus the appendix also has a physiologic function, and serious interference with the function of the cecum and the appendix may give rise to disease. This is instanced by the fact that the majority of cases of appendicitis are associated with the digestive process. Disturbed cecal and appendiceal digestion has an effect upon the small intestine and the latter in turn upon the

cecum and the appendix. Irritation and inflammatory changes in the appendix, through the superior sympathetic mesenteric plexus, produces pain in the abdomen and especially in the region of the umbilicus and of the epigastrium. This is what causes confusion in the early localization of the lesion and gives rise to the belief that the patient is suffering from gastric indigestion or a disturbance in the upper part of the lower intestine.

The nerve supply of the appendix is through the superior mesenteric plexus, the branches of which go to the appendix accompanying the ileocolic artery. The usual site of pain in chronic appendicitis is at McBurney's point and is the result of reflex action. Irritation of the appendix is reflected back to the plexus which is related by branches to that part of the spinal cord giving off the lower dorsal and upper lumbar nerves. Sherren states that this reflex pain occurs oftenest in the area of distribution of the eleventh dorsal nerve. Pain may thus be referred to the right thigh, the right testicle or the right lumbar region. Referred pain in appendicitis often confuses the situation, no better example of which is the confusion of the pain of appendicitis with neuralgia of the lower intercostal nerves.

Disturbed cecal and appendiceal digestion results in lack of proper secretion of the succus entericus and lowering of the activity of the lymph nodes, causing loss of control of the bacteria that swarm the cavity of the cecum and the appendix. Although in pathologic conditions the colon bacillus is the surgeon's arch enemy, in its proper place it serves a useful purpose in effecting the disintegration of undigested matter, but when the organs are unhealthy it leads to the production of toxins. In cecal appendiceal indigestion, stasis and constipation occur on account of the abnormal amount of succus entericus. Fermentative changes take place in the cecum and the appendix which with absorption of toxins causes the diarrhea met with in some instances. Disturbed cecal and appendiceal digestion, in the presence of pus organisms, produces sequelæ that have a serious effect on the appendix resulting in chronic disease.

Indigestion causing discomfort in the alimentary tract is a very vague and loosely employed term. The appendix and cecum having a rich supply of glands of Lieberkühn, they both play a part in digestion. Appendiceal indigestion or dyspepsia is therefore the proper term, since interference with the digestive function of the appendix and the cecum will, as a matter of course, sooner or later give rise to disease ending in a chronically diseased appendix. If we remember that the glands of Lieberkühn are by far more numerous and better developed in the ascending colon, the cecum and the appendix than in the small intestine, we shall appreciate the import of cecal and appendiceal digestion.

McEwen clearly states that in most appendices removed at operation one sees that the surface is covered with the glands of Lieber-

kühn in an active state of secretion, during health, thus making the secretion of the appendix alone a valuable aid to digestion.

Chronic appendicitis is seen as a catarrhal or interstitial or obliterative (appendicitis obliterans) type, the last being the terminal stage of the interstitial. In its gross as well as its microscopic pathology the chronically diseased appendix very much resembles the chronically diseased gall bladder, even to enlargement of the lymph nodes at the base of the appendix, within the mesoappendix and the mesocecum or mesocolon, corresponding to enlargement of the cystic node at the neck of the gall bladder and the nodes along the common duct; the nodes in both conditions show microorganisms, and thus emphasize the danger of extension of infection by way of the lymph vessels. In the diseased appendix, as in the diseased gall bladder, infection is also carried by way of the tributary veins of the portal system of which the appendicular veins are a part. Bacteriologic study of the nodes in relation with the diseased appendix shows the hemolytic streptococcus in about 50 per cent of the cases. (Research Laboratory, Lankenau Hospital.)

Chronic appendicitis is as much an entity as chronic peptic ulcer or chronic cholecystitis. Those who cry loudest against this entity I fear form their opinions, in many instances, from deductions made from their study of the outside of the abdomen. Chronic appendicitis cannot always be diagnosed by the radiologic-clinician or the radiologist since not all chronic appendices retain bismuth or barium, for example, the interstitial type if at all advanced, or if it contains concretions, and the chronic catarrhal type whose lumen is often obstructed by concretions or by stricture. To make the diagnosis of chronic appendicitis dependent upon Roentgen ray findings is a delusion and a snare. Clinical experience and clinical diagnosis still count and mechanical diagnosis will not and cannot win over clinical diagnosis. While this may be the age of machine power over man power, the art of diagnosis still rests upon human power.

Chronic appendicitis frequently comes on insidiously, without pain, but with more or less indigestion and abdominal discomfort. Not all chronic appendices are the result of a previous acute attack, but may be due to a low-grade intestinal infection. Chronic appendicitis the result of a previous acute attack or attacks is followed by intermittent attacks of mild pain, epigastric distress, due to reflex pylorospasm, occasional nausea and more or less gaseous distention particularly of the small intestine, a syndrome that at times is impossible to differentiate from a mild chronic cholecystitis or a typical duodenal ulcer or a mild chronic pancreatitis. It is in this type that palpation will elicit rigidity of the overlying abdominal muscles, tenderness and oftentimes an enlarged appendix. The second type is that in which the symptoms appear insidiously with indigestion,

slight abdominal discomfort, and mild intestinal distention, where violent exercise or fatigue causes lower right abdominal discomfort and not infrequently, pain. Here gentle palpation by skillful touch will reveal characteristic findings: some loss of flexibility of the overlying abdominal muscles, tenderness and not infrequently a palpable appendix. The palpable appendix must not be mistaken for the wall of the cecum, especially if it contains soft feces, the semilunar line, or the lateral border of the rectus muscle. The stumbling point in making the diagnosis by palpation is that many a doctor practises medicine a lifetime and never acquires the sense of touch. Touch, I consider, the greatest asset in making the physical examination, and in the case of the diseased appendix it is far superior to any Roentgen ray examination. Gentle touch, skillful touch, refined touch make for much more in the diagnosis than the heavy hand or the Roentgen ray can accomplish.

The diseased appendix, like the diseased gall bladder and the diseased duodenum causing pylorospasm, causes a spasm of the muscle fibers of the ileocecal junction and leads to lower right abdominal discomfort. The chronically diseased appendix causes referred pain, the point of reference depending upon the position of the appendix and the direction in which it points. In the diagnosis, not only of chronic but of acute appendicitis as well, the position of the appendix and the direction it assumes have a most important bearing.

The most common positions of the appendix, as I have frequently pointed out, are lateral to and behind the cecum and colon, in the pelvis, beneath the terminal ileum and mesentery and pointing downward and backward to the left, above the terminal ileum and mesentery pointing upward and to the left, to the mesial side of the cecum and colon and anterior to the cecum and colon. I see a number of cases where pain is referred to a point immediately above Poupart's ligament on the right side and where a diagnosis of commencing hernia, on account of what is believed to be succussion on coughing, is made. These patients are tender to pressure over the area of referred pain with loss of normal flexibility of the overlying muscles as compared with the opposite side, and upon careful examination do not present any definite signs of hernia. At operation, the appendix is found inflamed while the inguinal canal is found normal. On the other hand, the two conditions are occasionally combined. It is the practice in the Lankenau Clinic, when possible, to remove the appendix through the hernial wound when operating for right inguinal hernia. This is practical in all but a few cases. The exceptions are where the cecum holds a high position and cannot be brought into the wound and where the appendix is retrocecal or retrocolic and adherent, or is in one or another of the possible positions making it inaccessible to attack through the

inguinal canal. In such circumstances, the appendix should be removed through a second incision. In practically all these cases the appendix is found diseased.

In removing the appendix through the hernial wound, great care is needed in tying off the mesoappendix, seeing that it is relaxed not tense, when the ligature or ligatures are applied, otherwise bleeding may occur after the cecum has been replaced. Furthermore, if the appendiceal stump is not thoroughly sterilized, contact with adjacent tissues may result in infection, defeating the object of the operation—the cure of the hernia. The only sure method of sterilization is amputation with the cautery at a white heat. If the appendix is diseased, as is usually the case, and one cannot be sure of his technique, it is better to make the usual appendiceal approach, than to attempt to take it out through the hernial wound.

Our experience in incidentally finding a chronically diseased appendix while operating for other conditions has convinced us beyond any question of doubt of the soundness of the statement that chronic appendicitis is not only an entity but an enemy as well to its possessor.

It will be seen how confusion may occur if the pain is referred elsewhere than to the neighborhood of the cecum. For example, where the appendix is located in the pelvis the pain is referred to the lower left abdomen. Furthermore, especially in children, if the cecum has not completely descended, doubt may be injected into the question.

Many of our operations include not only the removal of a chronically diseased appendix left at a previous abdominal operation, but also operation for acute attacks including all varieties, many of which are admitted with a lethal peritonitis. With few exceptions, not removing the appendix in all abdominal operations, especially of the lower abdomen, I know has been the cause of many a fatality in a subsequent attack of acute appendicitis. In the hands of the skilled operator, this little additional piece of work adds no risk. We should remember that to relieve pain and prevent death are our two chief missions. We are all familiar with the condition of acidosis most often seen in children, many of whom suffer repeated attacks. A deranged alimentary canal is most often the cause, so that taking out the chronically diseased appendix is the logical thing to do as a preventive. This is made clear by what I have said in describing the function of the appendix. Many of you are constantly advising removal of the tonsils and teeth for otherwise indeterminable conditions, but you are not advising removal of the chronically infected appendix, which I believe to be indirectly responsible for more deaths than all of the above combined.

The conditions most commonly confused with or mistaken for chronic appendicitis are chronic peptic ulcer, chronic cholecystitis,

a mobile splashing and tender cecum with or without coloptosis or visceroptosis, and stone in the right ureter. Other conditions are carcinoma of the cecum, tuberculosis of the cecum, tuberculosis of the peritoneum, of the lymph node at the junction of the ileum and the cecum, diverticulosis, chronic diverticulitis, retroperitoneal lymphangitis, effusion within the psoas sheath, early psoas abscess, chronic right-sided pyelitis, stricture of the right ureter, stone in the ureter, and a chronic lesion of the right uterine appendage. Of these various conditions, with the exception of carcinoma or tuberculosis of the cecum, the ones most frequently encountered are pyelitis and chronic disease of the right uterine appendage. In early carcinoma and tuberculosis of the cecum, before there is a definitely palpable mass, the differentiation can only be made with certainty, by incision, inspection and touch; therefore, when in doubt, operate. Where there is a small palpable mass, I rarely have a Roentgen ray examination made fearing it will not be correctly interpreted and that operation will be deferred, resulting in the disaster of delay. Better operate and find nothing than operate and find too much, is a dictum that bears endless repetition. Multiplicity of consultations and of roentgenograms have, in many instances, taken away the advantage of early operation. Opening the abdomen in order to dispel doubt and reveal truth is certainly attended by less risk than waiting for a hair-splitting diagnosis, to decide the question. In this age of mechanical and laboratory diagnosis, the surgeon's hand is too often stayed by consultants who shoot at, but too often miss the bull's eye. In early carcinoma of the right colon or tuberculosis of the cecum, before there is metastasis, operation is curative while delay robs the patient of the chance of cure. I cannot stress this too strongly, for at the present day not to take out a chronically diseased or a doubtful appendix is exposing the patient to unjustifiable risks. Even if all the symptoms of which the patient complains are not cleared away by removal of the appendix, the patient's assurance against future acute attacks, metastatic infection and death more than warrants the interference. I am free to confess I am not in sympathy with my colleagues who oppose this stand.

It is taken for granted that the surgeon who removes the chronically diseased appendix must be competent to excise the terminal ileum, the cecum and ascending colon should the case prove to be carcinoma or tuberculosis of the cecum, or carcinoma of the colon. I fear that the operation of taking out the appendix is thought to be so simple that it frequently is done by one not capable of handling a more serious condition. However, this is not an argument against what I am pleading for.

Pyelitis, as well as stricture of the ureter and ureteral stone, can, be differentiated from appendicitis by a careful physical examination, chemical study of the urine, by cystoscopy, Roentgen ray,

pyelography and uretography. When, as often happens, the two conditions, stone in the ureter and chronic appendicitis, are present the appendix can be taken out through the incision for exposing the ureter, which should be an extraperitoneal one.

In case of confusion between chronic appendicitis and chronic disease of the right uterine appendage, the history of vaginal discharge together with vaginal and rectal examination will usually suffice to make the differentiation.

Differentiation between a chronic noncalculous cholecystitis and a chronically diseased high-lying appendix is oftentimes difficult and occasionally impossible, nor does cholecystography always help us. It is my experience that if careful study of the history with painstaking physical examination does not make the diagnosis, it will usually not be made by Roentgen ray study.

Gall-bladder indigestion, in contrast with the indigestion of chronic appendicitis, presents characteristic symptoms such as discomfort, nausea, belching of gas soon after eating, and in the more aggravated cases, vomiting. Thus one can often make a differential diagnosis from the history alone. It is well known that greasy and highly-seasoned food aggravates the gall-bladder patient, while this is not necessarily true of the appendiceal patient. Careful consideration of these and other points brought out in the history will act as guides in reaching a correct conclusion. I often wonder whether, with our present-day accomplishments, we are not neglecting the old and valuable methods in diagnosis.

Next to the history, the physical examination is of greatest diagnostic importance especially in the presence of a mass or of definite rigidity and tenderness. In the physical examination, sight and touch play the chief rôles. In both acute and chronic disease of the abdomen, by having the patient lie perfectly flat upon the back, and by observing the contour of the anterior abdominal walls during normal and forced breathing, much information is obtained, such as irregularities, increased pain caused by deep breathing, and the absence of movement of part of or of the entire abdominal wall.

In the differentiation between chronic noncalculous cholecystitis and a high-lying chronic and tender appendix, when the patient gives a typical history, palpation, if properly made, usually will help to locate the pathology. In the enlarged chronically diseased gall bladder palpation detects a swelling movable with respiration which, with tenderness and overlying rigidity makes the diagnosis comparatively certain. In the absence of a palpable gall bladder, light pressure over the normal site of the fundus, that is to the right of the border of the rectus muscle, and immediately below the junction of the ninth costal cartilage and rib will elicit rigidity and tenderness, their degree depending upon the degree of the gall-bladder inflammation. With the fundus brought in contact with the abdominal wall, having

the patient breathe deeply and hold his breath, finger pressure will increase the pain. I attach much importance to demonstrating the site of pressure pain in the differentiation between gall-bladder and appendiceal disease.

In the tender high-lying appendix, the tenderness can be traced from below upward, the tender area corresponding to the position of the appendix. In addition to the appendiceal tenderness, the enlarged appendix can often be palpated.

Cholecystography and Roentgen ray examination have not given me as much satisfaction in differentiating between the chronic gall bladder and the chronic appendix, as have a carefully taken history and a carefully conducted physical examination. The latter I consider paramount in the diagnostic study of surgical abdominal ailments. Roentgen ray examination in the diagnosis of chronic appendicitis has never appealed to me since the Roentgen ray report stresses the presence of tenderness in the manipulations in carrying out the examination, much if not more, than retention of a part of the barium meal.

In the female, the symptoms are, not uncommonly, more marked at the menstrual period. More important than the symptoms, however, are the physical findings, such as tenderness over the location of the appendix, with a certain degree of rigidity or stiffness of the overlying abdominal walls. To elicit these signs requires skillful touch born of large experience in abdominal diseases.

That the chronic appendix is a menace is evidenced by the fact that it is found diseased in practically all cases of abdominal disorders such as chronic cholecystitis, and chronic peptic ulcer, so that it undoubtedly is a factor in the etiology of these conditions. In the cases where the appendix has been taken out, it is altogether possible that it was the original focus of infection, for it must be admitted that the appendix is the most common site of intra-abdominal infection, so that it is a common site from which infection migrates.

It is not an uncommon experience in badly infected appendiceal cases to have the kidneys involved, as evidenced by hyalin and granular casts, albumin, and so forth, in the urine, and to find that in most of these cases when the appendiceal infection has been eradicated the kidney condition clears up; also where the infection has lasted a long time the kidneys have become permanently damaged. Assuming this to be so, does not the infected appendix play a rôle in the etiology of Bright's disease? In my opinion, this is as likely as that neglected scarlet fever leads to chronic nephritis.

I believe that many cases, where a chronically diseased appendix is responsible for the abdominal discomfort, are now being treated for indigestion, dyspepsia, mild colitis and intercostal neuralgia, and so forth. The history of the case with careful physical examination

and a knowledge of the many conditions that can simulate a chronically diseased appendix will solve the riddle in nearly all such instances. I am daily demonstrating this in the Lankenau Clinic, in the study of the pathology of the living. Medication and colonic lavage will not cure the chronically diseased appendix any more than medical drainage of the gall bladder will cure chronic gall-stone disease. The money misspent in Roentgen ray examinations and laboratory investigations in the study of abdominal ailments is appalling, and the results disappointing, to say the least. I have these studies made only where the patient's history is not clear and the physical examination is negative.

I classify all cases of appendicitis as either acute or chronic. The acute includes the catarrhal, interstitial, subacute, relapsing, perforative, gangrenous and phlegmonous types. In any or all of these varieties, there are constitutional symptoms, pain, nausea or vomiting or both, increased pulse, temperature and leukocytosis; also abdominal rigidity, tenderness and often a palpable mass.

To differentiate these types of the acute appendix is not always possible and the attempt to do so only complicates the situation. The two words, acute appendicitis, include all the types, and hair-splitting diagnosis often does not get the patient anywhere, except perhaps, to the grave. So with chronic appendicitis, the clinician who can differentiate the various types has not yet been born. There are clinicians, however, who impress their patients with their ability to differentiate between a terminal neuritis of the lower intercostal and iliohypogastric nerve and chronic appendicitis, and are bold enough to declare that pain in the lower right abdominal quadrant is more often the result of such, than of a chronically diseased appendix. This declaration will, I am sure, be the cause of many deaths from acute attacks superimposed upon a chronic appendicitis.

The fact that all patients who are operated upon for chronic appendicitis are not relieved of all of their symptoms does not prove that there is no such entity. I challenge my opponents to prove their claim by specimens from the living subject, and to show that lurking infection in the appendix is not responsible for some, if not most, of the upper abdominal conditions which the surgeon is constantly revealing at the operating table.

I do not deny the rôle of other sources of focal infection, such as the tonsils, the teeth and the sinuses, and so forth, but I do claim that compared with the appendix their rôle is an inconspicuous one, otherwise we surgeons would not find upper abdominal inflammation and appendiceal inflammation associated in practically all cases. At least, I may say, that this has been my experience in the many thousand abdominal operations that I have performed.

CHRONIC BRONCHIECTASIS IN CHILDHOOD, WITH OBSERVATIONS ON EARLY DIAGNOSIS.

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BRONCHIECTASIS, whether affecting adults or children, represents but one aspect of the composite picture of chronic, nonspecific pulmonary disease. Three types of this condition have been described in the pediatric literature: (1) A congenital form, variously reported as "congenital cystic formation of the lungs" or "atelectatic bronchiectasis," which is found rarely in stillborn children; (2) an acute type, called "bronchiolectasis" and observed in the terminal bronchioles of marasmic infants; (3) finally, that type—most commonly recognized—which occurs as the result of chronic pulmonary infection. The latter type, which is of prime importance in any study of thoracic diseases, will be dealt with in this paper. From the records of the Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia for the years 1923 to 1928, I have selected 53 cases* which I have felt demonstrated this condition in children under thirteen years of age, and these have been used as the basis for conclusions. Several additional cases have been excluded which were due to foreign bodies of long residence, though it is conceivable that they very properly might be added to this group. I have also excluded cases in which bronchiectasis complicated proven pulmonary tuberculosis.

There is a paucity of literature on the subject of bronchiectasis in children and even those articles reviewed were almost barren of references concerning its relative frequency. Vital statistics and hospital records give no clue to its incidence. Half of the cases reported here were revealed only when the histories and roentgenograms of children variously classified as chronic pneumonitis and so forth were carefully restudied. In this series 31 were males and 22 were females and death occurred in 4 cases. Willis Lemon¹ of the Mayo Clinic recently reported 63 cases of bronchiectasis in children which occurred in 15,500 admissions during a five-year period and noted 3 mortalities. Experienced observers, such as Landis,³ or Davidson and Pearson,² agree that the incidence of bronchiectasis is much greater than anyone has reported to date.

* The case histories here reviewed were selected from the records of the University and Children's Hospitals. The courtesies extended by Dr. J. C. Gittings, Dr. J. P. C. Griffith, and Dr. Alfred Hand are hereby acknowledged. Dr. Henry Pancoast and Dr. Eugene Pendergrass rendered considerable aid in the selection and interpretation of roentgenograms. Dr. Chevalier Jackson and Dr. Gabriel Tucker extended the aid of the Bronchoscopic Clinic in the review of their records.

Etiology. The exact etiology of an essentially chronic disease such as bronchiectasis is often difficult to determine. There are so many serious infectious diseases of early childhood which may profoundly damage the respiratory tract, and they often follow one another with such surprising rapidity that more than one may be responsible for the pathologic changes in the bronchi. Bronchopneumonia seems to be the most frequent antecedent of bronchiectasis in this series, being the causative factor alone in 23 cases; however, 26 other cases gave the history of secondary attacks of pneumonia, and several of the children had suffered as many as 5 recurrences. Lemon's¹ report shows that pertussis was the most frequent precursor, occurring in 27 of his 63 cases, but in this series pertussis was the definite forerunner in only 14, although 17 additional children had contracted this disease at some time during their lives. Measles accounted for 9 cases but had occurred in 18 others, influenza incited 3 cases and 2 cases had no precursor other than repeated upper respiratory-tract infections. Diphtheria with laryngeal stenosis and six years of cannulation was responsible for 1 case, and poliomyelitis with resultant paralysis of the diaphragm, atelectasis and secondary infections for another.

However, the exact rôle of any special diseases in the causation of bronchiectasis is a matter of conjecture for the real etiologic factor is a chronic infection so deeply implanted in the bronchial walls and supporting tissues of the lung that there results stagnation of secretion, increased intrabronchial tension from cough and finally ectasis of tubes which have lost the resilience of their structural framework.

Following the report of Mullin⁴ attention has been directed frequently to the apparent causal relationship between diseases of the nasal accessory sinuses and bronchiectasis. The impression gained from study of these cases and other reports is that one cannot evaluate accurately the entire significance of the upper respiratory-tract infections in the production of such an advanced pathologic entity as bronchiectasis. All but five of the children reported in this series gave histories of repeated upper respiratory infections since early infancy. In 38 there was demonstrable evidence of residual processes, such as sinusitis, pharyngitis, otitis and septic tonsils, not to mention lymphadenopathy. Thus, one must either assign the cause of bronchiectasis in almost all cases to these diseases, or one must conclude that they play a concomitant part only in the maintenance of residual infection. My conception of the natural history of bronchiectasis is that there is a common gradient of respiratory-tract pathology down which one proceeds following bronchopneumonia, a disease capable of implanting infection deep in the structures of the lung.

Given a child with rickets, undernutrition and a poor environment, and the ground is prepared for the seeds of such an infection. Various other acute febrile disorders follow rapidly, leaving in their



FIG. 1.—(Case I.) Roentgenograms of the anteroposterior and lateral aspects of Case I before treatment, showing moderate bronchiectasis at the right base and interlobar pleurisy. Note obliteration of the right lower angle of the cardiac outline.



FIG. 2.—(Case I.) Roentgenogram showing anteroposterior and lateral aspects of Case I after injection of lipiodol.

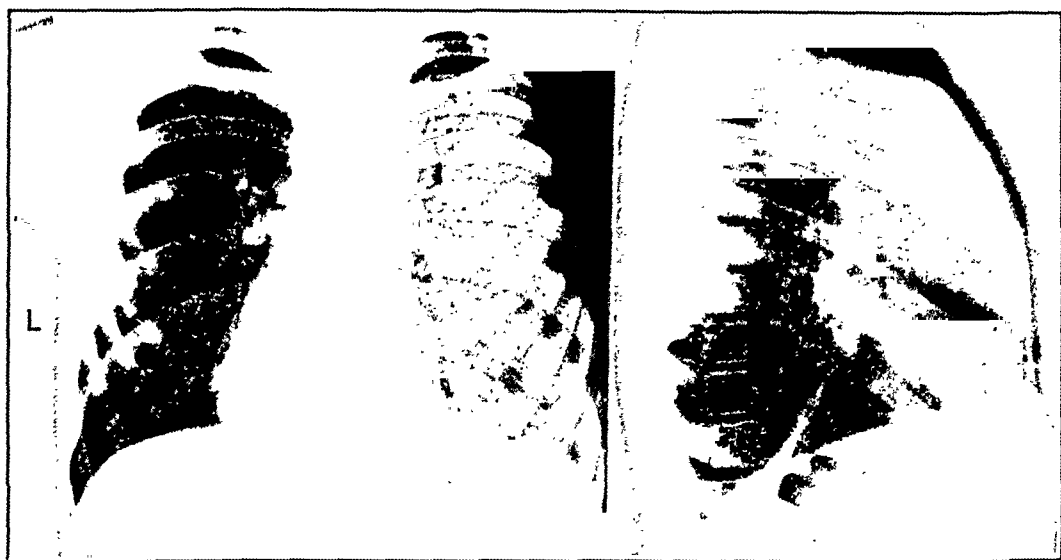


FIG. 3.—(Case I.) Roentgenograms taken after six bronchoscopic treatments of Case I. Shows considerable improvement.

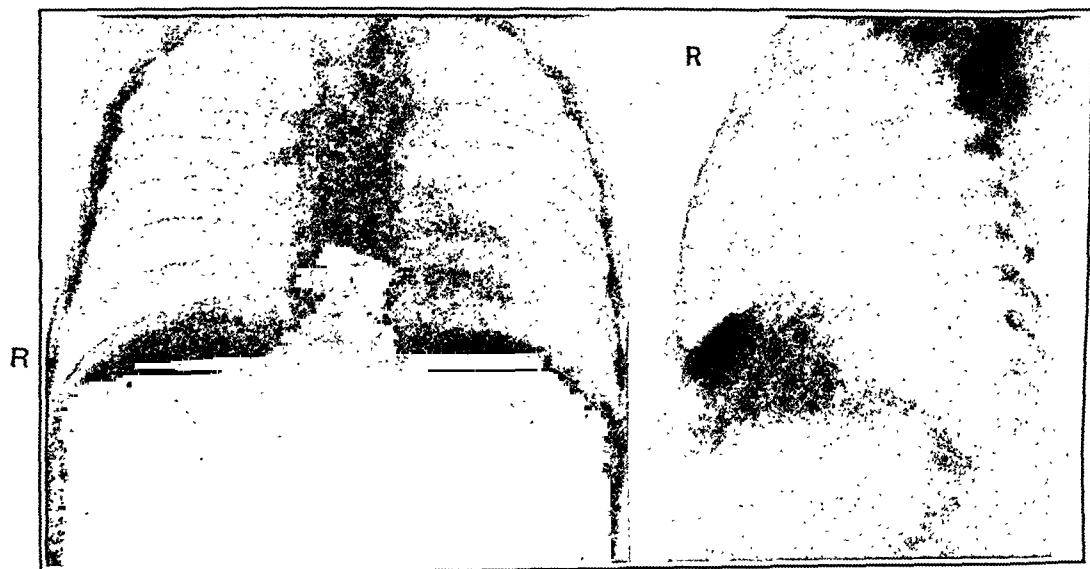


FIG. 4.—(Case II.) Roentgenograms showing very early signs of bronchiectasis and thickened interlobar pleura. Note the cordlike trunk shadows extending to the periphery of the right base.



FIG. 5.—(Case III.) Roentgenograms showing early evidence of bronchiectasis at both bases. Note the huge trunk shadows extending to the periphery, especially in the lateral view.

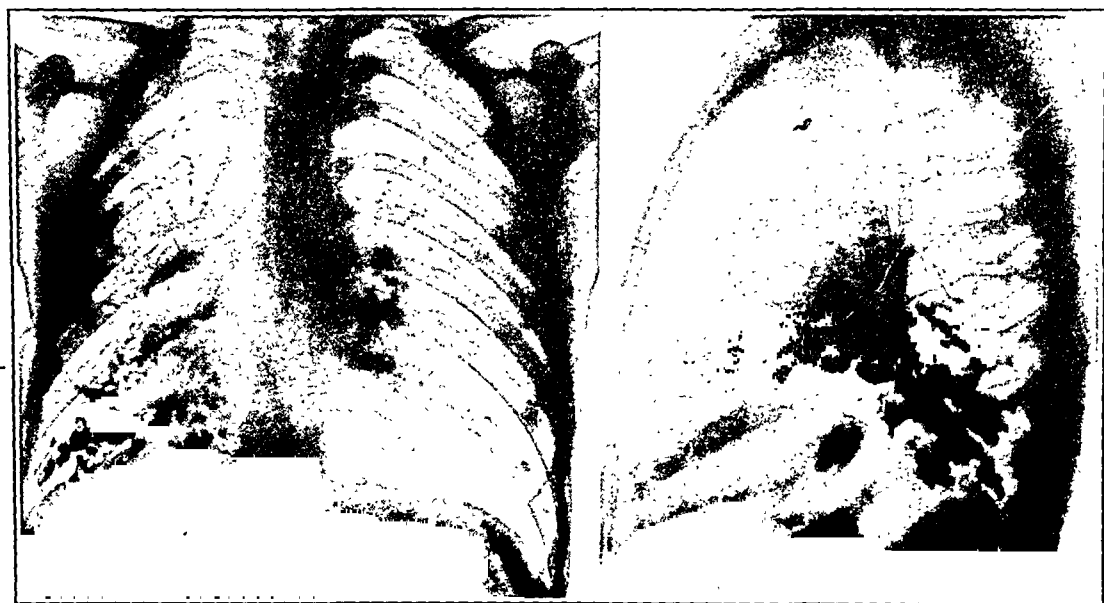


FIG. 6.—(Case IV.) Roentgenograms taken after lipiodol instillation in an advanced case. The saccular type of bronchiectasis can be seen, especially in the lateral view.



FIG. 7.—(Case V.) An advanced case which resulted fatally. Autopsy showed adhesive pleurisy, bronchiectasis and some abscess formation. Streptococcus in blood culture.

wake structural lesions in the lungs and septic pockets in the sinuses and tonsils. A vicious circle is then established and the child is never free from recurrent respiratory diseases which have either started in the lungs and augmented the upper-tract sepsis, or have been initiated in the sinuses and tonsils and have increased the intrinsic damage to the bronchial walls. Saccular bronchiectasis, abscess formation, carnification and localized empyemata are end results of the process.

Study of the causative organisms is of interest. These have been determined in all of the 27 cases which were "bronchoscoped." In no other way can an accurate investigation be made. The streptococcus was the dominant organism in 50 per cent of the cases studied, the staphylococcus in 12 per cent, *Micrococcus catarrhalis* in 20 per cent, the pneumococcus and influenza bacillus in 8 per cent each. Diphtheroid forms occurred in practically all cases, and from every case at least four organisms were recovered.

Pathology. Enough has been written concerning the final pathologic picture of chronic bronchiectasis to make it unnecessary to rehearse such a description here. It is my intention to emphasize the morbid changes which occur in early cases and not the gross lesions seen at the autopsy table. The pathology of early bronchiectasis can be seen through the bronchoscope and deduced from roentgenograms. These changes are of interest since they give clues to early diagnosis. Roentgenograms of potential cases show slight interstitial and peribronchial fibrosis at the bases only, with diaphragmatic pleurisy as an almost constant finding. Endoscopic protocols report slight annular dilatation of the bronchi, infiltration of the mucosa with loss or distortion of the glands, and residual secretion even after exhaustive coughing. This secretion is tenacious, yellow-green, mucopurulent and difficult to aspirate. Such a picture differs tremendously from the more advanced one usually presented in textbooks, lacking the saccular dilatation of the tubes, the destruction of mucosa and the quantities of foul-smelling pus.

Clinical Considerations. The principal symptom for which these children were brought to the hospital was cough. This cough was variable, being spasmodic and nonproductive in most of the early cases, and was incited particularly by change of position or exercise. When the sputum was produced in early cases it was yellowish, mucopurulent and tenacious. Of course, all sputum was lost in the younger children since it was swallowed. The cough in advanced cases was described as rattling and periodic, though at intervals, there would be severe paroxysms, which would culminate in the production of foul pus.

No other disease of the lungs causes hemoptysis more frequently than bronchiectasis. Blood spitting was reported as a symptom in 27 of these cases, and in 2 cough and hemoptysis preceded all

physical signs and roentgenologic findings by several months. Anorexia, asthenia and remittent fever were also repeatedly noted, while failure to gain was almost a constant symptom.

The physical signs are, broadly speaking, those of fibrosis of the lower lobes, with or without evidence of cavitation, and accompanying bronchitis. The most striking feature of these signs is their protean character. Thus, a child may show dullness, distant breath sounds and only occasional râles at one time, but at another, following a paroxysm of coughing, may present tubular or cavernous breathing with bubbling râles and wheezes. Usually there is some demonstrable impairment to the diaphragmatic function. In some the signs are those of massive pleurisy or effusion, with deformities of the chest and displacement of the heart. In early cases in which fibrosis is not extensive lagging of one diaphragm, slight impairment of the percussion note, prolongation of expiration and moist râles are the sole changes. In these a diagnosis should be made only after consideration of the history, physical signs, roentgenograms and the report from the bronchoscopist.

Definite clubbing of the fingers was noted in 29 of these 53 cases, but it is my impression that minor deformities of the nails occur more frequently, and are overlooked in all but advanced cases.

Many children, for whom no fever was reported as a symptom, showed evening rises of temperature when under hospital observation, but this disappeared following bronchoscopic and postural drainage.

The roentgenologic findings are of immense diagnostic importance. Usually an affirmative report is based upon the finding of obliteration of the lower right angle of the heart by thickened bronchial trunks which extend like cords to the periphery, and the recognition of impaired diaphragmatic action. Many advanced cases show uniformly increased density of the whole lung due to pleurisy, and can only be diagnosed accurately after the injection of lipiodol. Unilateral involvement was seen in 62 per cent of the cases, but one feels confident that bilateral disease will prove more frequent with the wider usage of lipiodol.

Complications. These children are especially vulnerable to recurrent bronchopneumonia, which, closely followed by pleurisy, is the commonest complication. Abscess of the lungs occurred in 7 of these cases and localized pneumothorax followed by empyema in 3. One case developed subcutaneous and mediastinal emphysema together with pneumothorax, but recovered uneventfully. One case only developed septicemia. Renal disease is apparently a noteworthy complication but no more so than in other suppurative conditions. Nineteen cases showed evidence of mild nephrosis, but 5 developed severe hemorrhagic nephritis though only 1 of the latter failed to survive. The Mantoux test was positive in only 11 of the older children, but there was no evidence at hand for connecting tuberculosis and bronchiectasis in a causal relationship.

Many of these children go about their ordinary affairs and their state of undernutrition is not recognized. Many times the initial examiner at the hospitals reported that the child under consideration was of normal development when the actual measurements proved that it was 12 to 18 per cent underweight and 1 or 2 inches under-height. Most of these cases were frail, undernourished and asthenic and a few even emaciated. Practically all showed some of the characteristic deformities of healed rickets. With only three exceptions, the whole group was below the normal standard for height and weight according to age and sex. The average subnormal variation for weight was 14 per cent, and the variation for the group ranged from 8 per cent above normal to 48 per cent below normal.

Anemia contributed to the debilitating effects of this disorder in 31 cases. In 25 the hemoglobin was below 55 per cent and transfusions were used in 18. These transfusions proved to be of great value, especially in increasing the general bodily resistance.

Illustrative Cases. CASE I.—D. T., a male, aged seven years at admission. No familial history of tuberculosis. Breast fed for nine months; solid food was introduced after twelve months and no rachitic prophylaxis was used. Pneumonia in 1921 and 1922 followed by measles, pertussis and varicella in rapid succession. Pneumonia in 1923 and 1927. Has had repeated "colds." Tonsillectomy in 1923. History of cough, dyspnea, daily fever and failure to gain. Showed an area of dullness, distant bronchial breathing and moist râles at the right base. Moderately clubbed fingers and 8 per cent undernutrition noted. No anemia or positive tuberculin test reported. Improved after six bronchoscopic treatments coupled with postural drainage, a balanced diet and heliotherapy.

CASE II.—E. L., a female, aged two years, nine months. She was examined first in the fall of 1926 and bronchiectasis has developed almost under observation. A premature baby, weighing $5\frac{1}{2}$ pounds, was never breast fed, but a well-known "patent food" was used. No cod-liver oil given until the age of twelve months and then rickets was marked. This child has had six attacks of bronchopneumonia, three recurrences of otitis media and constant sepsis of the maxillary and ethmoid sinuses. Her physical signs are similar to those of asthmatic bronchitis, but sensitization tests were negative. Shows only 50 per cent hemoglobin (Sahli) and is 30 per cent underweight. Cannot walk yet. Roentgenogram shows interlobar pleurisy and the evidence of early bronchiectasis.

CASE III.—I. R., a female, aged eight years. Breast fed for eighteen months; no solid food until fourteen months and never received antirachitic treatment. Severe attack of pertussis at eighteen months, said to have lasted six months; mild measles at five years; three attacks of bronchopneumonia and is almost never free from upper respiratory-tract infections. Tonsillectomy was performed at six years of age. Nonproductive cough, nasal obstruction and tardy development since infancy. Physical signs are slight impairment at the bases, lagging of the right diaphragm and occasional showers of moist râles. No anemia; is tuberculin negative, but is 10 per cent underweight. Roentgenogram shows right interlobar pleurisy with increased prominence of the trunk shadows draining the right base. Marked improvement of cough, physical signs and nutrition after three endoscopic treatments, supplemented by postural drainage, correction of her diet and adequate heliotherapy.

CASE IV.—P. C., a male, aged eight years at the first admission. The onset of paroxysmal, nonproductive cough followed influenza and bronchopneumonia. In addition he has had four other attacks of pneumonia and an attack of severe pertussis. Was diagnosed tuberculosis and sent to a sanatorium once but is tuberculin negative to 1 mg. of O. T. The cough became rattling and productive of foul pus five years ago. The signs in the chest are those of massive bilateral bronchiectasis with displacement of the heart. Roentgenograms after use of lipiodol show the saccular type of bronchiectasis on both sides. In spite of extensive involvement he has no anemia, but is 14 per cent underweight. This boy has been subjected to 250 endoscopic drainages in the past four years and shows scarcely any improvement.

CASE V.—M. V. N., a female, aged two years. Was fed on condensed milk for two years and never received cod-liver oil. She had several colds during her first year and two severe attacks of bronchopneumonia from which she has never recovered. The cough was rattling and occasionally productive. The physical signs in the chest were flatness on the left, dullness on the right, with many areas of amphoric or bronchial breathing and bubbling râles. Thorax markedly deformed. This child was emaciated, weighing only 14 pounds. The sinuses and oral cavity were badly infected and she had clubbed fingers. The blood showed marked anemia and contained nonhemolytic streptococci. This child died before she could be treated and the autopsy showed advanced bronchiectasis and abscess cavities with adhesive pleurisy.

Treatment. If all cases suspected of having suppurative bronchitis were bronchoscopically treated and not filled with worthless cough mixtures, bronchiectasis would actually be a rarity. Between treatments the children should have postural drainage, breathing exercises, plenty of nourishing food, cod-liver oil, fresh air and adequate heliotherapy. A comprehensive program utilizing these agents should be planned for every case and no other remedy seems to be of any use. In advanced cases vaccine therapy should certainly be tried, using an autogenous vaccine prepared from the endoscopic drainage. One cannot help pointing to the necessity of early diagnosis as an aid to efficient treatment. This is well typified by Cases I and IV, described above. The former is practically relieved after six treatments and the latter scarcely helped by 250.

Chart I shows an analysis of the 30 cases which were bronchoscoped or autopsied and in which the diagnosis cannot be questioned. The symptoms, signs, roentgenologic findings, bronchoscopic findings or autopsy findings are tabulated so as to point out the fundamental factors leading to the diagnosis. Chart II exhibits an analysis of 23 cases included in the series due to the facts that the histories, physical signs and roentgenologic findings were similar to those cases tabulated in Chart I. These cases were not studied bronchoscopically. It is hoped that in this way that the type of case to be suspected of bronchiectasis may be pointed out, and the importance of bronchoscopic study and pneumography may be emphasized.

CHART I.—ANALYSIS OF SYMPTOMS, PHYSICAL SIGNS, ROENTGENOLOGIC AND BRONCHOSCOPIC FINDINGS FOR
THE 30 CHILDREN WHO WERE BRONCHOSCOPED.

Cases	Symptoms					Phys. signs				Rales				Breath sounds				Roentgen ray signs				Bronchoscopic findings		
	Cough	Hemoptysis	Fever	Sweats	Wgt. loss	Expectoration	Club fingers	Under wgt.	Emphysema	Dry	Moist	Bubbling	Bronch. ves.	Bronch. chnl.	Tubular	Amphoric	Cavernous	Density bases	Incr. bronch. trunk	Cavity shadow	Pos. lipiodol shadow	Dilated bronchi	Suppur. bronchi	Cavity
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
17	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
21	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
22	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
23	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
24	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
25	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
26	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
27	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
28	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
29	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
30	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Cases 18, 19, 20, 21 resulted fatally. All of them were autopsied and the lungs showed dilated, sacculated bronchi with cavity formation. Case 18 showed marked hyperplastic pleurisy with carnification of the right lung. Both lungs in this child were riddled with cavities containing purulent material. All of these cases showed areas of dullness at the bases and limitation of the movement of one or both diaphragms.

CHART II.—ANALYSIS OF FINDINGS FOR THE 23 PATIENTS NOT BRONCHOSCOPED.

Cases	Symptoms					Phys. signs			Râles		Breath sounds			Roentgen ray signs			Remarks
	Hemop-ty sis	Fever	Wgt. loss	Sweats	Expec-tor ation	Club fingers	Emph-ysena	Under wgt.	Moist	Bub- bling	Bron- chial.	Tubu- lar	Cav- ernous	Dens- ity bases	Incr. bronch. trunks	Cav- ity	
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Pleurisy
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Interlobar pleurisy Severe case
5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Pneumothorax
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Sinusitis mastoiditis
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Nephritis
14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
17	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
19	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
20	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
21	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
22	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
23	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

Cough was a symptom in all of these cases. In none of these cases were dry râles or bronchovesicular breathing noted. None of these children were bronchoscoped and none died. All of these cases showed dullness at the bases and limitation of diaphragmatic action.

Summary. 1. A series of 53 cases of bronchiectasis in children under thirteen years, occurring in a five-year period, is reported and analyzed. However, the opinion is advanced that this condition is far more common than is usually supposed.

2. Bronchopneumonia, pertussis and measles are the common antecedent factors in the production of bronchiectasis, since they carry infection deep into the frame work of the bronchi and lungs. Disease of the accessory sinuses is thought to be a concomitant factor in maintaining a state of sepsis.

3. An attempt has been made to demonstrate the protean nature of the disease and to correlate the physical findings with the pathologic lesions, especially in early cases.

4. Evidence has been presented showing the damaging effect of the disease on the nutritional state of the affected children.

5. A rational mode of treatment is outlined, which includes drainage of the pus-filled bronchi and care of the general health of the patient. Early diagnosis is urged to make more efficient such a therapeutic program.

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RETROPHARYNGEAL ABSCESS IN INFANTS AND CHILDREN.

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THERE is a prevailing impression that retropharyngeal abscess is uncommon in infants and children, and that when it does occur, the diagnosis is easily and readily made. Our experience, however, leads us to believe that the condition more frequently escapes recognition than any other acute disease in childhood. In fact, every child in our series was brought to our attention with the condition undiagnosed and had been treated for from one to three weeks with no suspicion of the correct diagnosis. This may perhaps be partly explained by the fact that when the general practitioner diagnoses the disease he refers the patient at once to a throat specialist. It is

the purpose of this paper to emphasize the relative frequency of retropharyngeal abscess in infants and children and to advance the methods employed by us in making a diagnosis of retropharyngeal abscess.

The history of retropharyngeal abscess dates back to Hippocrates who mentions it in his book *On the Prognostics*.¹ "Those quincies . . . such as . . . are attended with pain, are swelled up, and have redness in throat are indeed very fatal. . . . It is much less hazardous when the swelling and redness are determined outwardly, but if determined in the lungs they superinduce delirium, and frequently some of these cases terminate in empyema." Galen,² in the second century, relates a case which occurred in his experience and which terminated in spontaneous rupture. From his manner of alluding to the case it appears that he had seen several examples of this kind, most of which ended fatally. Centuries later, Morgagni² described a case which caused death by rupture into the trachea. In 1785, Bleuland² mentioned that his master, Van Doeveren, had seen a case which terminated fatally.

C. Fleming³ was the first to make a study of retropharyngeal abscess. He published his results in 1840, two years prior to Verneuil⁴ who also gave an accurate description of the disease. Roustan⁵ (1869), Gautier⁶ (1869), and von Schmitz⁷ (1873) added their studies. Gautier called the affection "angine phlegmoneuse," Roustan, "adenite suppurée retropharyngienne;" the latter, therefore, may be classed among the first to view the disease as a suppurative lymphadenitis. These early observers, while conceding that a retropharyngeal lymphadenitis might precede a retropharyngeal abscess, thought that this sequence was the exception. It was the elder Bokai⁸ who first viewed retropharyngeal abscess as invariably coming from a lymphadenitis—a conception which experience has shown to be correct.

Anatomy. The retropharyngeal lymph nodes were first described by Mascagni. In his work, "*Vasorum lymphaticorum corporis humani hist. et iconographi*" (1785, page 63), he described them as "glandulæ . . . quae ad latus internum carotidis internæ resident prope ipsum ingressum in canalum coroticum." Most anatomists (Merkel, Luschka, Sappey) called them retropharyngeal glands, although Henle described them as the deep facial glands.

There is considerable disagreement as to the number of glands included under the term retropharyngeal lymph nodes. Poirier and Cuneo⁹ state that usually they are two in number. Most's⁴ very accurate researches on the topographical anatomy of these glands led to the following conclusions: In the newborn, there is in the majority of cases only one gland; in a few cases, two; very seldom more. Topographically they belong to the deep cervical chain of glands.

These nodes, embedded in loose areolar tissue, are located behind the pharynx at the level of the atlas and at the junction of the

posterior and lateral walls of the pharynx. Anterior to these glands is the posterior wall of the pharynx. Posteriorly they are separated from the lateral masses of the atlas by the rectus capitus anticus major muscle. Externally they are in relation with the constrictors of the pharynx and through these with the internal carotid artery. Internally, they are nearly 2 cm. distant from the midline of the pharynx. The retropharyngeal glands receive afferents from almost all the collectors of the mucosa of the nasal fossæ and their accessory sinuses, the lymphatics of the nasopharynx, those of the Eustachian tubes and perhaps some of the lymphatics of the cavity of the tympanum. The efferent vessels of the retropharyngeal glands empty into the internal glands of the deep cervical chain. Since the retropharyngeal glands do not drain the palatine tonsils, infections of the latter can reach these glands only indirectly, namely, through involvement of the neighboring pharynx. After the first year of life, they undergo retrogressive changes, but persist, as a rule, until later in childhood, as is evidenced by the number of cases of retropharyngeal abscesses that occur in children over one year of age.

Pathogenesis. Anatomical studies explain the progress of a case of retropharyngeal abscess. The first stage of the disease is infection of one of the points drained by the retropharyngeal glands. This usually is an adenoiditis, though rarely rhinitis, sinusitis, or otitis may also usher in the disease. When the infection spreads to the retropharyngeal glands there results an adenitis with an accompanying periadenitis which frequently is followed in twenty-four to forty-eight hours by suppuration. At times, however, the disease does not progress beyond the stage of lymphadenitis, pus formation does not occur and resolution takes place.

Retropharyngeal abscess may conveniently be classified as primary and secondary. The most frequent variety is the primary or idiopathic (Bokay¹⁰). It is preceded, as a rule, by a nasopharyngitis, although occasionally the accessory nasal sinuses and the middle ear are the portals of entry. The secondary retropharyngeal abscesses follow infection of the upper cervical vertebræ (Pott's disease), or migration of pus from a superficial cervical adenitis or, what is still rarer, a metastasis from a distant abscess. A rare cause of secondary retropharyngeal abscess is a cavernous sinus thrombosis. According to Eagleton,¹¹ the postpharyngeal suppuration originates from retrograde thrombophlebitis of the veins communicating with the cavernous sinus and the pharynx. In fact, Eagleton states that when a retropharyngeal abscess is encountered during the course of an attack of otitis media in a patient over eighteen months of age cavernous sinus should be suspected. At times retropharyngeal abscess follows trauma; the traumatic type is encountered only exceptionally and is usually due to a foreign body, as a rule a fish bone, lodging in the posterior pharynx, though occasionally tonsillectomy is the etiologic factor. Numerous examples of each variety have been reported in the literature.

Sex. This is not an important factor, the cases being equally divided.

Age. Retropharyngeal abscess is a disease of childhood. The reason for this is that the retropharyngeal glands undergo retrogressive changes after the first year of life. Von Schmitz⁷ found no, or at most one, gland in this region after the third year. The researches of Most⁴ agree with this view. The smaller glands behind the pharynx are never found in adults and the main lateral retropharyngeal glands atrophy until they are no larger than a bean; and are, therefore, easily overlooked.

Retropharyngeal abscess is most frequent between the ages of two months and four years. In Bokay's¹⁰ series 94 per cent of the cases occurred during the first three years of life. Vas,¹² continuing this series, found 59 per cent of the 1054 cases occurring in the first year of life; 35 per cent between the first and third and less than 1 per cent after the seventh year. Guthrie¹³ in a series of cases reported the following statistics:

	Cases.	Per cent.
0 to 1 year	7	35
1 to 2 years	4	20
2 to 3 years	3	15
3 to 4 years	2	10
4 to 5 years	1	5
5 to 6 years	1	5
6 to 7 years	2	10
Total	20	

Babbitt¹⁴ found that 60 per cent of his 50 cases of retropharyngeal abscess occurred in the first year of infancy:

	Cases.	Per cent.
0 months to 6 months	8	16
6 months to 1 year	25	50
Second year	13	26
2 to 2½ years	1	2
2½ to 4 years	1	2
4 to 6 years	1	2
6 to 10 years	1	2
Total	50	

Similar findings are recorded by Frank.¹⁵ Seventy of his 74 cases occurred in children under ten years of age and 90 per cent in children under three years of age. In our series of 55 cases, 22, or 40 per cent, occurred in infants under one year of age; 25 cases were found between one and two years of age; the remaining 8 were distributed as follows:

	Cases.	Per cent.
0 to 1 year	22	40.00
1 to 2 years	25	45.00
2 to 3 years	2	3.63
3 to 4 years	1	1.81
4 to 5 years	2	3.63
5 to 6 years	2	3.63
6 to 7 years	1	1.81
Total	55	

Eighty-five per cent of our cases were, therefore, under two years of age. This agrees with former statistics. The oldest child that we have seen with this affection was seven years of age and the youngest five weeks of age. The great majority of our cases occurred in children under two years of age.

Season. The disease occurs most frequently in the spring and winter months. The reason for this is evident: upper respiratory infections are most common in these months.

Associated Diseases. Retropharyngeal abscesses occur occasionally during or after the acute infectious diseases. Of Bokay's¹⁰ 926 cases, 14 occurred during an attack of scarlet fever; one during measles and two during diphtheria of the pharynx. The abscesses complicating the exanthemata are, as a rule, malignant and have a tendency to burrow downward into the mediastinum. Syphilis is mentioned by some authors as an etiologic factor. Bokay¹⁰ observed 8 cases due to syphilis. These are, however, the exception. The influence of constitutional diseases, such as rickets or the scrofulous diathesis, on the development of retropharyngeal abscess is indefinite and very doubtful. The only associated or complicating diseases in our series were the initial nasopharyngitis and the subsequent otitis media.

Bacteriology. In 1894 Koplik¹⁶ studied 8 cases of retropharyngeal abscess bacteriologically and succeeded in isolating a streptococcus in all. In one case he found, in addition the *Bacillus lactis aërogenes*, which was probably a contamination from the mouth. These findings have since been repeatedly corroborated.

Symptoms. The onset is usually insidious. In the majority of cases, there is a preceding nasopharyngitis, which produces a wide range of symptoms; after a lapse of from two to four days the first symptoms of retropharyngeal abscess appear. The time elapsing between the appearance of the first symptom and the time of diagnosis varies. It may be only two days and it may be three weeks. The average is about ten days.

Most textbooks mention difficulty in swallowing as the first symptom. This has not been our experience. The earliest symptoms in our cases were either restlessness, fever or an enlarged cervical gland. We wish to emphasize particularly the presence of a unilateral cervical adenitis. The enlarged gland is usually situated at the angle of the jaw at the posterior border of the sternocleidomastoid muscle. In 2 cases, the enlarged gland was anterior to the angle of the jaw and almost in the midline. The presence of an enlarged gland in these regions should always lead one to suspect a retropharyngeal abscess and to exclude it, if possible, by the only absolute method of diagnosis, namely, palpation of the throat.

Difficulty in swallowing is a very important symptom, although it must be emphasized that it is not a very early one and occurs relatively late in the disease. Young infants show it by refusing all

food. Thus, an infant will take the breast very eagerly, suck it a few times, then let go, throw the head backward, eject the milk from the mouth and cry bitterly. One must be on guard not to attribute such a refusal of food to colic. We have seen a four-month-old infant, suffering from retropharyngeal abscess, treated for one week for colic, because it appeared to be in pain when taking the breast.

At first the pain on swallowing is caused by inflammation. Only later, when the abscess obstructs the pharyngeal cavity, does the mechanical factor come into play. Mechanical obstruction is most marked in the rare case where the abscess is in the midline; it is also prominent in lateral abscesses that are so large that they approach the midline. In our series of cases, not one abscess was found directly in the midline. All were lateral. This fact may account for the absence of dysphagia as an early and predominating symptom. Infants may become dehydrated very rapidly unless proper measures are taken to supply them with fluid. Dystrophy may result if the abscess is of long-standing. Since the pharynx is smaller in infants than in older children, the younger the child the more marked will dysphagia be. Occasionally, however, nourishment is not refused even though the condition is advanced.

The voice, too, changes. It loses its natural tone and becomes nasal in quality. When the child cries or talks, the voice assumes a peculiar muffled quality as if there were a hot potato in the mouth. This becomes more and more definite as the affection progresses. The voice change differs from that found in palatine paralysis following diphtheria, in that in the latter disease the voice is flatter, weaker, and lacks the deep gurgling qualities found in cases of retropharyngeal abscess.

Respiratory difficulty is present in almost every case and occasionally causes diagnostic errors. Careful observation of the type of respiratory embarrassment will often give a clue to the level of the abscess. If the abscess is located in the upper part of the pharynx, nasal breathing is impossible and the child becomes a mouth breather. An abscess at the level of the epiglottis will cause respiratory difficulty simulating that found in laryngeal stenosis, due to diphtheritic laryngitis or to foreign body in the larynx. Only when the possibility of retropharyngeal abscess is kept in mind and the throat is palpated is the true condition revealed. Due to the difficulty in swallowing, mucus collects in the throat and causes the rattling and stertorous breathing so frequently heard. In fact, the snoring, gurgling respiration during sleep is one of the most constant symptoms of retropharyngeal abscess. All these symptoms are aggravated when the patient is in a horizontal position. Again, the younger the patient and the more rapid the course of events, the more pronounced are these findings.

Torticollis is a symptom found in nearly every case and, when

present, should always lead one to rule out retropharyngeal abscess before a search is made for other causes. In one of our cases, torticollis was the outstanding symptom and was present for six weeks. It was so marked that roentgenologic examinations had been made to rule out vertebral pathology. This symptom was present in 80 per cent of our cases. Early in the disease there is a definite stiffness of the neck. A little later the head becomes inclined toward the affected side and in the last stages the neck is held immovable and backward to facilitate breathing.

The temperature is very rarely high. In most cases it ranges between 100° and 102.5° F. In only one of our cases was the temperature elevated above 103° F.

Physical Examination. When the child is brought for examination, one notes at once that he looks ill. As a rule, the head is held to one side, the mouth is open and dribbling is present. Rarely, facial paralysis is noted. When retropharyngeal abscess is suspected a careful examination of the glands of the neck should be made. Usually only one gland is enlarged. It may be situated anterior or posterior to the sternocleidomastoid muscle. At times, however, a whole chain of glands may become enlarged and late in the disease they may become matted together. When this occurs, the mass is very large and extends well down into the neck. When only one gland is involved, the enlargement may be so small as to escape superficial examination. If, however, the thumb and forefinger are hooked about the anterior and posterior borders of the sternocleidomastoid muscle the slightest increase in size can usually be detected. The glands, whether small or large, are usually hard; rarely, fluctuation occurs late in the disease when the abscess has ruptured outwardly.

It is necessary to have a clear conception of a normal throat in infants and children in order to determine, from the brief glance that is afforded the examiner, whether pathologic changes exist or not. Inspection of the throat in infants is rarely conclusive. In older children, difficulty is encountered in the examination because of trismus. The pushing forward of one pillar is one of the most constant signs found on inspection and one that may easily be overlooked. At times also a slight edema of the soft palate may be noted on the involved side. The edema, however, never reaches the extent found in peritonsillar abscess. Frequently the mucous membrane of the throat appears dry and congested. The mucosa covering the swelling is at first red and later, as suppuration occurs, the redness fades and the pharyngeal wall becomes pale and finally yellowish. When the abscess is large enough the soft palate and uvula are displaced laterally and forward. In cases where tonsillectomy has previously been performed the mass may be seen behind the anterior pillar, filling in the empty tonsillar space.

Frequently inspection reveals nothing and resort to digital

examination must be made to establish the diagnosis. In young infants, this offers no difficulty. In older children, care is necessary to prevent injury to the examiner's finger through biting. A mouth gag should not be used since sudden death, due to asphyxia, has been reported following its use. Our procedure is to use a metal finger which is placed on the index finger of the left hand and inserted between the upper and lower jaw at the first and second molars. This suffices to pry the mouth open wide enough to admit the index finger of the right hand which is swept about the pharynx. In the stage of lymphadenitis one finds to one side of the midline a tender, firm, resistant mass, smooth in outline, varying in size from a bean to a hazelnut. If suppuration is present, the mass feels elastic and boggy. When an abscess is present, the vertical and lateral extent is noted. The whole procedure should take only a few seconds. When done in this manner we have never seen any ill effects from digital examination. Occasionally, the prominence of the body of the seventh cervical vertebra is marked and unless care is taken it may be mistaken for lymphadenitis. In fact, this mistake was made in one of our cases. The deeper location and the bony hardness of the vertebra should prevent error. We wish to emphasize that all manipulation should be done gently to prevent rupture of the abscess and resulting suffocation of the patient. Thus, Koplik¹⁷ reports a case in which death followed within a few hours after pus was aspirated from an abscess which burst as a result of rough digital examination. Rarely, collapse follows digital examination.

The following table is an analysis of the symptoms recorded and of the signs observed in our cases. As may be seen, fever, restlessness and enlarged cervical glands occurred in every case. The fever in nearly every instance was of moderate degree. Voice changes were found in only a small number of cases; this may be attributed to the fact that the abscess in most of our cases had not reached large proportions.

Symptoms.	Cases.
Fever	55*
Restlessness	55
Cervical adenopathy	55
Respiratory difficulty	41
Difficulty in swallowing	35
Torticollis	44
Mass in back of throat:	
Lateral	55
Medial	0
Retropharyngeal abscess	53
Retropharyngeal lymphadenitis	2
Complicating otitis media	8

* Temperature 102° F. or less in 49; 102° F. or more in 6.

Complications and Sequelæ. If the abscess is left to itself, it may pursue any one of four courses: (1) It may burst spontaneously and

drain into the larynx. This is not uncommon, Bokay, Sr., having seen it nineteen times in 144 cases. The danger of this is the possibility of the pus gaining entrance into the tracheobronchial tree and causing sudden death, due to asphyxia; or multiple abscesses of the lung with fatal termination may result. Indeed, Babbitt¹⁴ believes that many cases of unexplained sudden asphyxia may be due to inspiration of pus from a ruptured retropharyngeal abscess. Myerson¹⁸ reported a case of spontaneous rupture of a retropharyngeal abscess which flooded the lungs. The child was given artificial respiration and a tracheotomy was done. A catheter attached to a suction apparatus was passed through the tracheotomy tube and the pus aspirated. The child made an uneventful recovery. We have observed several cases of spontaneous rupture with recovery, but we have never seen asphyxia resulting from rupture. It may be assumed that rupture has occurred in a case of retropharyngeal abscess when there is a sudden disappearance of the enlarged external glands and an immediate amelioration of symptoms. (2) The pus may burrow inwardly instead of being evacuated through the pharynx, dissecting the tissues laterally to the side of the neck behind the large vessels and the sternocleidomastoid muscle, and appear at the posterior triangle of the neck. If the abscess ruptures through the surrounding prevertebral fascia it may present itself anteriorly to the sternocleidomastoid muscle in the anterior triangle of the neck. (3) Instead of burrowing laterally the pus may extend downward along the prevertebral fascia into the lower part of the neck. This complication has been reported by Mercier.¹⁹ In his patient, the pus made its way through the tissues of the neck and opened at the level of the clavicle. (4) Rarely, the pus is guided behind the esophagus into the posterior mediastinum. A very rare route for the escape of pus is reported by Szmurl.²⁰ In his patient, the abscess burrowed through the internal auditory canal into the cranial cavity.

A relatively infrequent and serious complication is erosion of one of the main bloodvessels in the vicinity of the abscess. The vessels most likely to be involved are the internal carotid artery and, to a lesser extent, the internal jugular vein and the vertebral artery (the latter only in cases secondary to tuberculous cervical spondylitis). There are several reports in the literature describing cases of fatal hemorrhage from the carotid artery,²¹ occurring immediately after incision of the abscess. In isolated cases²² it has been possible to avert a fatal outcome by an immediate ligation of either the common or internal carotid artery. Not always, however, is the source of bleeding evident. Thus, Wishart²³ reports the case of a child eighteen months of age who had two severe hemorrhages from the mouth which were assumed to be of gastric origin. At the postmortem examination a large retropharyngeal abscess with erosion of the internal carotid artery was discovered. In one of our fatal cases,

the cause of death was hemorrhage due probably to an erosion of the internal carotid artery. This occurred in an infant six months old, who, a week after an attack of nasopharyngitis, developed a retropharyngeal abscess. This case was referred to a nose and throat surgeon who opened the abscess with a sharpened finger nail. As the finger was removed there was a violent gush of blood from the mouth and the child died within a few minutes. We have never encountered a case in which the internal jugular vein was involved. Mosher,²⁴ however, described a case of retropharyngeal abscess which ran a septic temperature after incision of the abscess. At the time of the second operation the internal jugular vein was found to be thrombosed and about 2 inches of the vein had sloughed away. Equally rare is erosion of the vertebral artery. It occurs only in cases of abscess secondary to vertebral inflammation and may cause fatal hemorrhage.

Prognosis. Retropharyngeal abscess is a benign disease if recognized early and treated properly, but dangerous and even fatal if unrecognized.

The time of diagnosis affects the prognosis: the earlier the diagnosis is established and proper treatment instituted, the better the prognosis. Operation should be deferred until definite fluctuation can be detected. We have had one fatality due to a failure to recognize the fact that a retropharyngeal lymphadenitis should never be incised before the stage of suppuration. This occurred in an infant eight months of age who, ten days after an attack of nasopharyngitis, refused food, cried when forced to eat, and snored while sleeping. Examination showed the cervical gland on the left side to be enlarged and tender. A firm, tender, mass was palpated in the left posterior wall of the pharynx. The mass was incised; after the operative interference the general condition became rapidly worse, swallowing became impossible, the temperature rose to 104° F., and attacks of cyanosis occurred. Four days after the incision the child died, presenting the picture of a profound sepsis.

The influence of constitutional disturbances or of accompanying infections on the prognosis is evident and needs no discussion.

As a rule, the mortality rate of retropharyngeal abscess is low. In Bokay's¹⁰ series there were 14 deaths in 317 cases. In our series of cases, the mortality rate was somewhat higher (7.3 per cent), 4 deaths occurring in a series of 55 cases.

Treatment. Treatment will depend entirely upon the stage in which the disease is first observed. If the patient is seen during the stage of lymphadenitis, mild alkaline sprays or gargles are indicated. Local applications of equal parts of glycerin and alcohol to the neck may be of use. Operative procedure is absolutely contraindicated in this stage. As soon as fluctuation is present the mass should be incised. In our cases the internal route was used almost without exception. External incision anterior to the sternocleidomastoid

muscle has also been advocated. According to Bokay, Jr.,¹⁰ this method of approach was first practised by St. Germain in 1872. In the hands of some men, it has given good results. Thus, Schmidt²⁵ treated 15 cases of retropharyngeal abscess (13 primary and 2 tuberculous) by the external route with no unpleasant incidents either during the operation or subsequently. We believe this method should be used only in cases secondary to cervical Pott's disease or in cases where the abscess is situated low down in the pharynx. In the latter case there is too much danger of some of the pus spilling into the larynx when the abscess is opened through the mouth. That the internal route is not without danger may be seen from reports of cases of sudden death following operative interference.

On the whole, however, immediate improvement follows incision. As a general rule, within twenty-four hours the glandular enlargement disappears to a great extent. The child shows a rapid improvement in its general condition and takes nourishment readily and eagerly. The improvement usually progresses until complete recovery takes place. A recurrence of symptoms after incision usually points to the closure of the operative opening and is an indication for reestablishment of drainage.

Summary and Conclusions. 1. A series of 55 cases of retropharyngeal abscess is reported and analyzed and the literature reviewed.

2. The condition is not uncommon in early infancy and childhood. It is more common in the first year of life than later. It is equally divided between the sexes and occurs most frequently in winter and spring, when respiratory infection is commonest.

3. Retropharyngeal abscess should be suspected in every case presenting an enlarged cervical gland and the diagnosis should be determined by a digital examination of the pharynx.

4. Retropharyngeal abscess is not an innocuous disease as demonstrated by the fact that the mortality rate was 7.3 per cent in our series.

5. The danger of operating in the stage of non-suppurative lymphadenitis as well as the dangers of not operating when fluctuation is present are pointed out.

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THE PANCREATIC TRIAD.*

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OUR previous experiments, performed on dogs with the help of E. W. and A. W. Boldyreff,¹⁻⁴ have shown that either a complete pancreatectomy or a severe loss of pancreatic juice through a fistula of the main pancreatic duct involve the following three pathologic conditions to which we have affixed the name "Pancreatic Triad:"

1. A rise in the percentage of the blood sugar (that is, a decrease in the content of glycolytic ferment in the blood).²
2. A decrease of the blood coagulability—apparently due to decrease in the content of fibrin ferment in the blood;³ and
3. The appearance of leukocytosis.⁴

Our numerous experiments on dogs have convinced us that complete loss of pancreatic juice (complete diversion to the outside) produces in general the same phenomena in the organism as does

* Reported to the American Physiological Society, Ann Arbor, Michigan, April 13, 1928.

complete pancreatectomy. In order to understand why this is true, one should recall that in normal conditions the pancreatic juice secreted into the intestine is immediately absorbed therefrom into the blood (as shown by our experiments—both those previously published and those described in this paper) and then enters the organism, supplying its tissues with all its ferments. But when the juice is discharged outside the organism, there is a lack of all pancreatic ferments. Thus, complete loss of pancreatic juice could be called physiologic pancreatectomy. One must believe that in anatomic (or surgical) pancreatectomy the chief cause of the diseased conditions following the operation is the deprivation of the body of the pancreatic juice.

In 1913, Dr. V. N. Vorobiev and I⁵ produced fistulæ of both pancreatic ducts (dog), so that all the pancreatic juice was flowing outside the body. Within twenty-four hours after the operation azoturia and glycosuria appeared, and the wound remained open for some time. (After the fistulæ were finally closed the dog quickly recovered.) All this, together with other known symptoms, is also observed in cases of complete pancreatectomy. We are still continuing these experiments and intend to treat such animals by the introduction of pancreatic juice through an intestinal fistula. I first recommended the use of pancreatic juice as a remedy in 1914.⁵ In my lectures at the Universities of Kyoto, Tokyo, Osaka and Fukuoka, I repeated this recommendation many times (1920-1921); Hedon's experiments confirm the correctness of such a view.⁶

The duration of the three phenomena which we have termed the "Pancreatic Triad" depends on the conditions of the experiment and varies in different cases from several hours to several days or more, as may be seen in Tables I and IV.

TABLE I.—RESULTS OF TOTAL PANCREATECTOMY ON A DOG.

No. of test.	Time in minutes.	Leukocytes in thousands per c.mm.	Blood-coagulation time in seconds.	Blood sugar in per cent.
Before the Operation (Normal).				
I	10.8	45	about 0.10
After the Operation.				
I	15	7.0	30	
II	150	12.0	75	
III	270	20.1	120	0.17
IV	540	20.3	180	0.21
	500 cc. blood taken out.			
V	600	..	240 (I)	

Experiment by E. Boldyreff and A. Boldyreff, February 26, 1925. Dog kept without food for twenty-four hours before experiment. Subcutaneous injection of 0.025 gm. morphin. Chloroform-ether-alcohol anesthesia.¹

Leukocytosis is notoriously easy to produce in the dog, and similar figures are the rule after narcosis and abdominal operation (see Krumbhaar⁷). The decrease in coagulability is striking.

Our new experiments (Table II) performed on many dogs and new observations made on several men have confirmed former ones and have shown that this pathologic triad may also be a consequence

TABLE II.—TOTAL PANCREATECTOMY POSTOPERATIVE RESULTS OF NEW DOG EXPERIMENTS (E. BOLDYREFF).

Dog N1a. Young female, 8,900 gr.

Time of observation	Normal (before operation)	5 hours postoperative	8 hours postoperative
Blood-coagulation time in seconds . . .	55	70	90
Leukocytes	6,500	19,700	
Blood sugar	0.095	0.112	0.132

Dog N2a. Female six months, 9,570 gr.

Time of observation	Normal before operation	12 hours post-operative	24 hours post-operative	31 hours* post-operative	44 hours post-operative	56 hours post-operative	72 hours post-operative
Blood-coagulation time in seconds	45	65	180	230	230	150	45
Leukocytes	6,800	23,100	17,000	18,100	..	7,900	6,800
Blood sugar	0.125	0.34	0.44	0.30	..	0.21	

Dog N3a. Male nine months, 13,620 gr.

Time of observation	Normal before operation	23 hours post-operative	28 hours* post-operative	47 hours post-operative	56 hours post-operative
Blood-coagulation time in seconds . . .	140	240	210	60	60
Leukocytes	8,800	26,000	20,000	15,100	21,000
Blood sugar	0.39			

* The time of first feeding after the operation.

of other defects in the function of the pancreas; thus, after a partial pancreatectomy, when about a quarter or a third of the gland is removed, no matter whether from the head or the tail, we observed a temporary appearance of all three symptoms (Table III).

In the other 8 cases of total pancreatectomy we obtained approximately the same results. In all our experiments described in this paper, the dogs were provided with an ample supply of drinking water.

In every case the tail of the pancreas (about 6 gm.) was removed. Removal of the head of the pancreas had the same effect, as was shown by our experiments.

TABLE III.—PARTIAL PANCREATECTOMY.

Dog No. 12.

Time of observation	Normal before operative	24 hours* post-operative	48 hours post-operative	56 hours post-operative	72 hours post-operative	144 hours post-operative	168 hours post-operative
Blood-coagulation time in seconds	30-45	30	360	405	150	45	45-50
Leukocytes . . .	7700	18,200	9300	8600	..	6800	8500

Dog No. 21.

Time of observation	Normal before operation	24 hours* post-operative	48 hours post-operative	72 hours post-operative	96 hours post-operative	120 hours post-operative	144 hours post-operative
Blood-coagulation time in seconds	30	60	75	180	35	30	25
Leukocytes . . .	4300	15,900	8700	9800	6700	5800	4700

Dog No. 29.

Time of observation	Normal before operation	24 hours* post-operative	48 hours post-operative	72 hours post-operative	96 hours post-operative	120 hours post-operative	144 hours post-operative
Blood-coagulation time in seconds	45	45	90	75	75	50	30
Leukocytes . . .	5400	8800	8900	6200	7300	6600	6400

Dog No. 30a.

Time of observation	Normal before operation	24 hours* post-operative	48 hours post-operative	96 hours post-operative	120 hours post-operative	144 hours post-operative
Blood-coagulation time in seconds	40	30	45	60	30	30
Leukocytes	6400	15,800	15,200	20,900	12,900	

* The time of first feeding after the operation.

In several cases the blood sugar was determined and an increase in its amount was found.

We next observed the triad in dogs as a consequence of both the ligation of pancreatic ducts or of the main duct only; even a temporary closure of both pancreatic ducts with clamps may produce the same phenomena (Tables V and VI). Last, and very recently, we have met with the above-mentioned triad (rise of blood sugar, leukocytosis, delayed blood coagulability) in cases of diabetes both

in dogs and in men (Tables VII and VIII). The figures obtained from experiments on dogs follow:

TABLE IV.—PANCREATIC TRIAD IN CASES OF PANCREATIC FISTULA.

Dog N5a.					
Time of observation	Normal before operation	72 hours post-operative	144 hours post-operative	168 hours post-operative	192 hours post-operative
Leukocytes	6900	5100	14,400	17,000	18,200
Blood sugar	0.1	0.14	0.16	..	0.24

On nine other dogs with pancreatic fistula, we obtained similar results.

In several dogs with pancreatic fistulæ, we observed that for several days after the operation the pancreatic juice did not secrete. During this time, the triad was absent on these dogs but it appeared as soon as the pancreatic juice began to flow abundantly from the fistula. As would be anticipated, we failed to observe the triad of symptoms following other types of operation on the digestive tract, as, for instance, gastric fistula, biliary fistula, etc. (Table V).

TABLE V.—PANCREATIC TRIAD UNDER VARIOUS CONDITIONS.

Dog.	Date.	Normal.	After a ligation of both pancreatic ducts.		
		3-28-27	4-1-27	4-5-27	5-3-27
6a	Leukocytes	7500	16,800	..	8500
	Blood coagulability in seconds	30	170	..	120
	Blood sugar	0.095	0.118	0.120	0.095

	Date.	Normal.	After ligation of main pancreatic duct.				1-30-24
		1-24-24	1-25-24	1-27-24	1-28-24	1-29-24	
7a	Leukocytes	6000	17,700 16,400	13,400	16,900	9500	8300

	Date.	Normal.	After operation for gall-bladder fistula.				
		3-28-27	3-31-27	4-1-27	4-5-27	5-12-27	
7b	Leukocytes	6600	6900	12,300	6600		
	Blood coagulability in seconds	25	25	25	25		
	Blood sugar	0.100	..	0.091	0.090	0.100	

Three cases are presented in Table V. In the Dogs 6a and 7a the pancreatic ducts were ligated and we observed the usual symptoms. Dog 7b, with a fistula of the gall bladder, was operated upon the same day as Dog 6a, with ligation of both pancreatic ducts. Although both operations were technically quite similar and were done nearly on the same anatomic region, Dog 7b (biliary fistula) showed no phenomena of the triad except for a brief leukocytosis, but Dog 6a showed the presence of all members of the triad.

TABLE VI.—PANCREATIC TRIAD (AFTER CLOSING BOTH PANCREATIC DUCTS).

Young Dog (8a), Ether Anesthesia.

	Normal	Ducts clamped	Ducts open
I Leukocytes	7100	12,200	9600
II Blood-coagulation time in seconds .	30	120	45
III Blood sugar	0.120	0.140	0.120
Time in hours	4	2

TABLE VII.—PANCREATIC TRIAD.

The Figures Obtained on Dogs 9a and 10a.

	Normal.	Diabetes.
I Blood sugar in per cent	0.100	0.615
II Leukocytes	6000	15,400
III Blood-coagulation time in seconds	30	120

This diabetic dog had a spontaneous (not experimentally produced) diabetes in mild form. Not infrequently we observed on this dog polyphagia, polydipsia, polyuria, glucosuria, hyperglycemia and convulsions with loss of consciousness. The dog has lived in the laboratory for more than three years and has given birth to two litters of puppies; the first litter consisted of one puppy and the second of two; one of which died shortly after birth. The condition of the dog sometimes greatly improves on a suitable diet. This dog is still living in the laboratory.

The following are the figures obtained by E. Boldyreff from tests on men:

TABLE VIII.—PANCREATIC TRIAD IN MAN.

	Normal	1	2	3*	4† cases
I Blood sugar in per cent	0.100	0.330	0.150	0.129	1.62(1)
II Leukocytes	8000	18,000	28,000
III Blood-coagulation time in minutes	2	3½	5½	7	

* After Glaser.¹⁴

† After Curtis.¹⁵

Up to this point in our discussion, we have presented data relating to pathologic conditions; but the members of our triad undergo parallel changes even in normal conditions during some physiologic processes.

Our experiments on dogs "outside of digestion," that is, in the absence of acid gastric secretion, have shown that the blood-sugar content, the blood-coagulation time and the number of leukocytes do not remain on the same level, but vary with marked regularity and uniformity. This appears to be in connection with the so-called "*periodical*" phenomena, starting in the digestive apparatus immediately at the close of digestion and continuing without interruption until digestion sets in again. The author has long ago established the fact that "outside of digestion" there is observed a "*periodical*" secretion of the pancreatic juice, and the periods of its secretion in dogs and in humans are thirty to fifty minutes ("*periods of work*"), with intervals of one to two hours ("*periods of rest*"). Fig. 1, 2 and 3. The existence of periodical activity in higher animals was confirmed in America by W. B. Cannon⁸ and by A. J. Carlson.⁹

In the accompanying Figs. (1, 2 and 3) we present the "*periodical*" variations observed in the members of the triad.

The phenomena of "*periodical leukocytosis*" are presented in Fig. 2 and Fig. 3 and are described in detail elsewhere.

All the data in this article indicate that certain blood changes result from depriving the body of pancreatic juice; whether this loss occurs from pancreatic fistula, pancreatectomy, injury or disease.

But we have also made experiments of an opposite nature, in addition to our observations with absorption of periodically secreted pancreatic juice. We introduced zymogene pancreatic juice into the blood and examined the blood before and after this introduction. These data will soon be published in detail elsewhere. Here I will quote just one of numerous experiments relating to the effect produced on the number of leukocytes by the introduction of pancreatic juice into the blood. With large doses, the number of white blood cells quickly decreases, but later leukocytosis appears (Table IX).

Introduction of active pancreatic juice into the duodenum produces the same effect (Table X).

We have also made experiments with substances, such as atropin, inhibiting the pancreatic secretion, and drugs like pilocarpin and nicotin which excite this secretion. The data obtained were in general analogous to all preceding findings. These experiments will also be published in a separate article devoted to the mechanism of the leukocytosis.

We see a marked decrease in the number of leukocytes after the introduction of pancreatic juice into the blood. We have made 10 such experiments; the results were the same in each case. I began these experiments in 1914 at the University of Kazan in collaboration with Dr. Sokoloff.

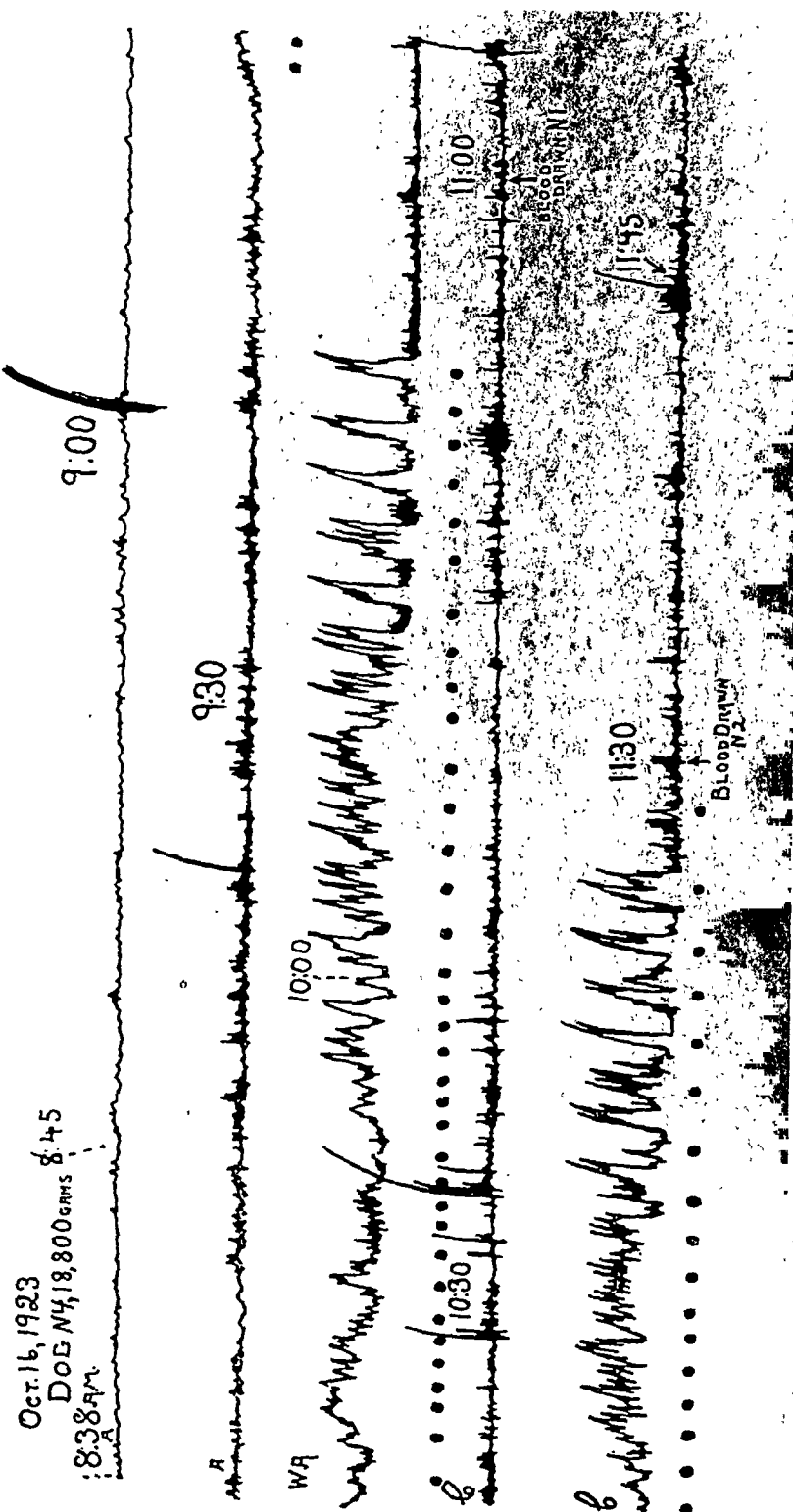


FIG. 1.—Periodical fluctuation in blood sugar evidently due to periodical increase and decrease in pancreatic glucolytic ferment in the blood. Curve 1 shows the relation between the manifestations of periodical activity of the digestive system outside of digestion and the changes of sugar content in the blood. It represents the record of periodical gastric contractions and periodical secretion of pancreatic juice (shown by dots) which occur simultaneously. Reaction in the stomach is indicated at the beginning of each line: (a) acid, (b) alkaline. The time marked every half hour. Blood sample No. 1 taken during the "period of rest" (absence of pancreatic secretion and gastric contractions) shows higher sugar, 0.094 per cent than sample No. 2 taken at the end of the "period of work" (during the secretion of pancreatic juice and gastric contractions), 0.075 per cent. Several experiments were made and similar results were obtained. The tracing is continuous from the left-hand top to the right-hand bottom. (Experiments on dog by E. Boldyreff.)

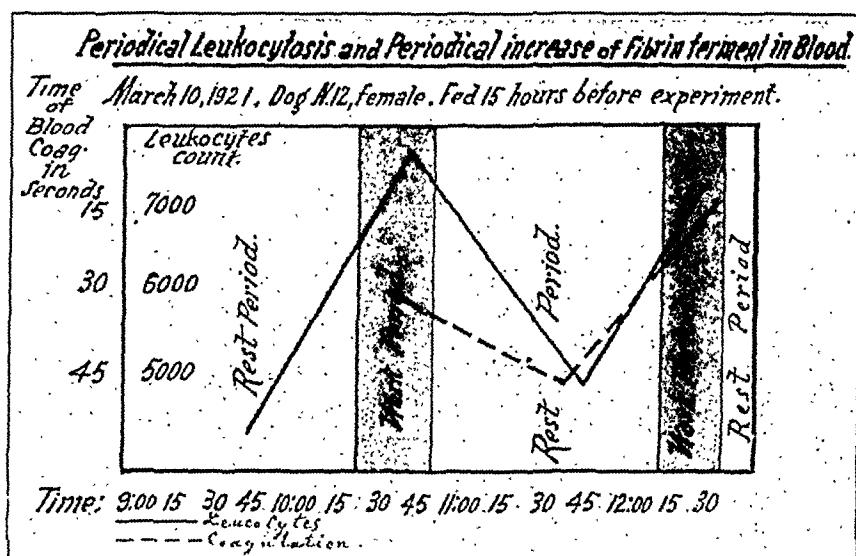


FIG. 2.—Periodical fluctuation in leukocytes number and blood coagulability. The periodical activity is presented here, but in a different manner from that on the Fig. 1. There the "periods of work" (third and fifth lines) and the "periods of rest" (rest of the lines) are shown just as they were registered on the kymograph during the experiment; while here both are shown schematically, but true to scale. Here we see that the first "period of rest" is somewhat longer than one hour and the first "period of work" (colored gray) slightly less than a half hour. Durations of the second "periods of work and rest" are about the same. The curves of the leukocytes and blood-coagulation rise during the "periods of work" and run practically parallel to each other.

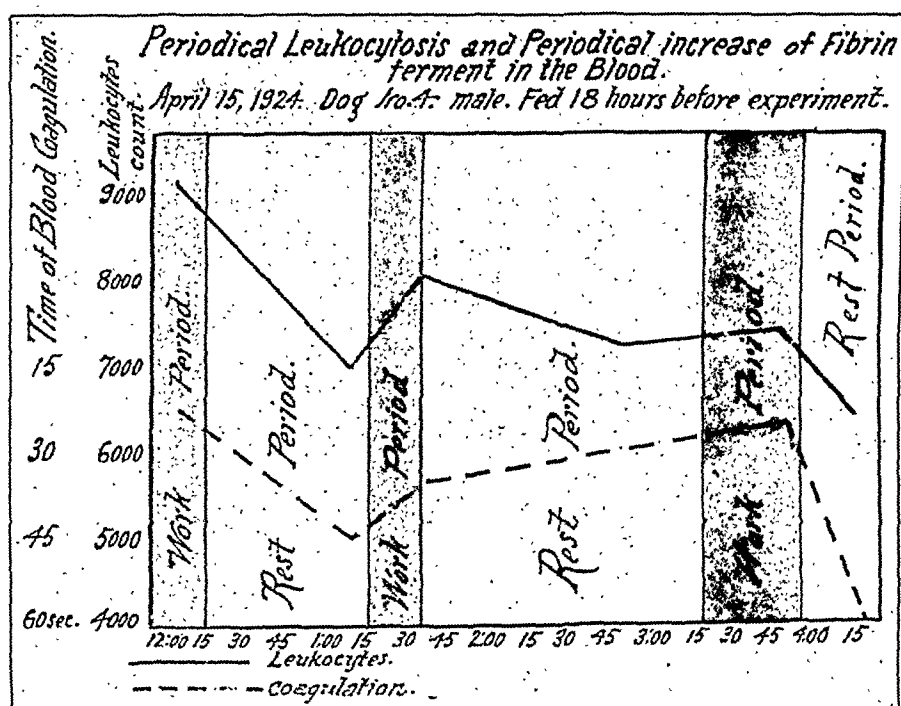


FIG. 3.—Periodical fluctuation in leukocytes number and blood coagulability. The same phenomena are presented as Fig. 2, but on a different dog. The experiment here was extended to include 3 "periods of work," and 3 "periods of rest."

The curves of leukocytes and blood coagulation similarly rise during "periods of work" and "periods of rest;" they also run almost parallel.

TABLE IX.—INTRODUCTION OF ZYMOGENE PANCREATIC JUICE INTO THE BLOOD.

(Dog No. 31. Pancreatic Fistula. Experiment by A. Boldyreff.)

Time after operation in days	1	2	4	5 Pancreatic-juice injected into blood 15 cc.	5 50 min- utes after introduc- tion of juice	5 2½ hours after in- troduction of juice
Leukocytes	13,400	9400	15,400	15,800	1500	5300
Blood-coagulation time in seconds	75	45	45	..	30	

TABLE X.—INTRODUCTION OF ACTIVE PANCREATIC JUICE INTO THE DUODENUM.

Dog. No. 7; weight 11,200 gm. Fed fourteen hours before experiment.

Fistulae of duodenum and stomach. Stomach and duodenum empty.

Experiment by A. Boldyreff.

12.15 P.M. "Period of rest" 10,300 leukocytes.

12.32 P.M. Introduced into duodenum 75 cc. "periodical" active pancreatic juice at 40°C. Until 3.30 P.M. reaction in stomach remained alkaline.

12.45 P.M.	10,800 leukocytes	} "period of rest"
1.00 P.M.	7,400 leukocytes	
1.20 P.M.	7,600 leukocytes	

We see that about half an hour after the introduction of the pancreatic juice into the duodenum the number of leukocytes was decreased by about 3000. Exactly the same experiments (in method and result) were performed eight times on two different dogs.

TABLE XI.—INTRODUCTION OF PANCREATIC JUICE INTO THE DUODENUM.

(Same dog as in Table X. The dog fasted throughout the experiment.)

III-31-24	10.27 A.M. "period of rest"	6800 leukocytes
	Introduction of pancreatic juice into the duodenum (moderate dose, about 50 cc.)	
IV- 2-24	5.00 P.M. "period of rest"	6000 leukocytes
	10.09 A.M. "period of rest"	9400 leukocytes
IV- 3-24	Introduction of pancreatic juice into duodenum (same dose)	
	5.24 P.M. "period of rest"	7600 leukocytes
IV- 4-24	10.51 A.M. "period of rest"	9000 leukocytes
	Introduction of pancreatic juice (same dose)	
IV- 4-24	5.52 P.M. "period of rest"	6300 leukocytes
	10.20 A.M. "period of rest"	8200 leukocytes
IV- 4-24	Introduction of pancreatic juice (same dose)	
	4.56 P.M. "period of rest"	5700 leukocytes

This pancreatic juice in all cases produced a decrease in the number of leukocytes.

Thus it would appear from the foregoing experiments that the introduction of pancreatic juice directly into the blood or into the duodenum produces a marked decrease in the number of leukocytes.

It has been observed that sometimes the use of substances acting on some one member of the triad affects the other members as well. Thus, subcutaneous injections of 10 units of insulin in dogs produced leukocytosis and decreased the coagulability of the blood.

TABLE XII.—ACTION OF INSULIN ON LEUKOCYTES AND BLOOD COAGULABILITY IN DOGS.

(Experiments by E. Boldyreff.)

	Normal	After insulin	Remarks
Leukocytes . . .	Dog 11a— 3,500 Dog 12a—11,000	Dog 11a— 6,300 Dog 12a—20,200	Such experiments were done on seven dogs, the results were identical in all cases.
Coagulability in seconds	Dog 11a—35 Dog 12a—45	Dog 11a—200 Dog 12a—130	

However, the appearance of these two members of the triad produced by the injection of insulin was of only short duration.

Here we see an example of the division of the members of the triad: after insulin the quantity of sugar in the blood decreases, but the coagulation time of the blood increases and the number of leukocytes augments.

As yet I refrain from analysing the causes of this phenomenon.

I would like to mention that Partos and Svec¹⁰ have recently obtained results quite opposed to mine: they report that the coagulation time decreases with the increase of sugar. I would not attempt to judge why they came to such conclusions.

In the most recent American literature, we find confirmation of some of our data. For instance Allan¹¹ of the Mayo Clinic, and Joslin, Root and White¹² as well as Curtis and Dixon,¹³ have found that in diabetes a pronounced leukocytosis is observed. Glaser¹⁴ also reported our complete triad in diabetes mellitus in man.

In this discussion, I refer only to the two new factors—leukocytosis and change in blood coagulability—found in my latest experiments performed in collaboration with E. and A. Boldyreff. These two pathologic factors were always observed in injury of the pancreas parallel with the third phenomenon which has long been known, namely, an increase of blood sugar in these conditions. Therefore, I have given to this association of three permanent phenomena the name "Pancreatic Triad," anticipating that in the course of time it may be increased by the discovery of new members.

We do not consider the name "*Triad*" as a definitive term for the complexity of all the pathologic phenomena observed by us and other authors connected with the affection of the function of the pancreas. Their number may increase later. For instance, we know

that removal of the pancreas or injury to its function involves usually a disorder of general metabolism and sometimes that of the fat metabolism in particular.

As yet, we refrain from any theoretical explanation of the problem; we only desire to offer our experimental data on dogs which are also confirmed by our observations on men, though as yet not very numerous.

In a special report, we expect to illuminate this problem in detail, by our experimental data and observations, as well as by the data in the literature.

But even now we believe that our pathologic triad can be of great help to the clinician for purposes of diagnosis and prognosis. Thus, if all the members of the triad are present in a pronounced degree, the diagnosis of some pancreatic disturbance is certain. Furthermore, in the presence of the triad, operative intervention is likely to be followed by unfavorable results: poor wound healing is probable, and even gangrene is possible. At any rate we know that just these results are being observed after removal of the pancreatic gland or complete diversion of its secretion. And the triad testifies to a more or less complete exclusion of pancreatic juice from the organism.*

Summary and Conclusions. The pancreas is an organ so important and so necessary to the general metabolism that its removal produces very complex conditions of disease in the organism. Serious pancreatic lesions also result in a varied and complex pathology, often very confusing. In this problem experiments on animals are of great help. We can either remove the pancreas wholly or partially, either head, tail or body, or save the gland, removing the pancreatic juice partially or wholly through a fistula or fistulæ. Finally, we can introduce into the animal's body an excess of pancreatic juice.

Clinicians do not have exact knowledge of the state of the pancreas, in what degree or quality it is impaired, or how the pathologic phenomena observed by them depend on this injury. We physiologists examine the animal in health and then bring about various well-known, strictly definite pancreatic destructions; we follow the development of various pathologic processes, ensuing as the result of these injuries. We can make anatomic studies of the

* If the question arises whether some infection may be producing the appearance of leukocytosis in this triad, I should answer as follows: All infections have a period of incubation, and the development of leukocytosis due to an infection (for example, after an operation) requires a long time, not less than twenty-four hours. But some of our data are obtained on nonoperated animals, known to be healthy (except for diabetes), and human beings with diabetes.

Besides, as a rule, our data were observed a *short* time (one or two hours or a little more), after a certain operation, and before any infection could develop to affect the animal.

Finally the "periodical" variations in the members of our triad in absolutely healthy dogs, also observed after very short intervals (about an hour), speak against the possibility of infection.

animal at any time. Therefore, it is easier for the physiologist to determine the basic facts of the physiologic activity of the pancreas and those pathologic phenomena which result from its various diseased conditions. Of course, the clinical data are extremely valuable for physiology, and a collaboration of the two is especially fruitful.

Complete loss of pancreatic fluid, either by pancreatectomy or fistulæ, produces a "Pancreatic Triad" of: (1) a rise in the percentage of blood sugar; (2) a decrease of the blood coagulability; (3) the appearance of leukocytosis. This is a complex useful in understanding the physiology of the gland, but also in diagnosis and prognosis.

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CLINICAL AND EXPERIMENTAL STUDIES ON CALCIUM AND CHOLESTEROL IN RELATION TO THE THYROID PARATHYROID APPARATUS.*

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THE discovery of the active principle of the parathyroid gland by Collip¹ has recently given impetus to further experimental investi-

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gation into the physiology of these endocrine organs. Much has lately been added to our knowledge of their function, more especially in means of delaying and preventing fatal tetany which usually follows their extirpation. A very excellent review of the present status of the physiology of these glands has recently been published by Dragstedt.²

This work was attempted with the idea of utilizing one of the methods of preventing or controlling tetany after parathyroidectomy, in studying the relationship of the thyroid to the parathyroid. One of these methods outlined by Jones³ required only preoperative administration of cod-liver oil, so that observation could be carried on without danger of results masked by treatment.

Sweet⁴ has observed that some of the symptoms of severe hyperthyroidism, such as tremor, nervousness and hyperpyrexia are somewhat comparable to the symptoms ascribed to parathyroid deficiency. Sweet⁴ also believes there is a definite relationship between calcium and cholesterol in the normal and pathologic animal and with these points in mind, the blood calcium and cholesterol were studied in the thyroparathyroidectomized dog and in patients with toxic thyroid disease.

Because of the close anatomic relationship between the parathyroid and thyroid glands, and because of their embryologic association, there may possibly be some physiologic connection between the two glands in thyroid disease. Gley⁵ advanced the theory that the parathyroids were embryonic thyroid tissue and introduced evidence which has not been convincing. Foster⁶ states that there is not a vestige of scientific evidence of the correlation of these glands.

Embryology. The parathyroid glands are epithelial bodies arising from the dorsal diverticula of the third and fourth pharyngeal pouches.

Two pairs of these bodies are formed and as they move caudad and as the ducts of the pharyngeal pouches atrophy they are set free and lie in close anatomic relationship with the thyroid gland. The pair arising from the third pouches lie, in the adult, one on each side of the inferior portion of the thyroid somewhat medially and frequently become embedded in the thyroid tissue. The pair arising from the fourth pouches are located on each side of the superior portion of the thyroid somewhat laterally and usually are outside the thyroid tissue.

The solid epithelial bodies become broken up into masses and cords of polygonal entodermal cells intermingled with bloodvessels. In postfetal life lumina appear in the cell masses and fill with a colloid material which is somewhat similar to, but not to be related to thyroid colloid material.²

The thyroid develops from three anlagen, a median and a pair of lateral outgrowths from the primitive pharynx. The median anlage comes from the floor of the pharynx, its site of origin being marked

in the adult by the foramen cecum of the tongue. It forms the isthmus and pyramidal lobe of the definitive thyroid. The lateral anlagen grow down from the ventral border of the fourth pharyngeal pouches and form the lateral lobes of the gland. The parathyroid glands are in close anatomic relationship with these lateral lobes in the adult.

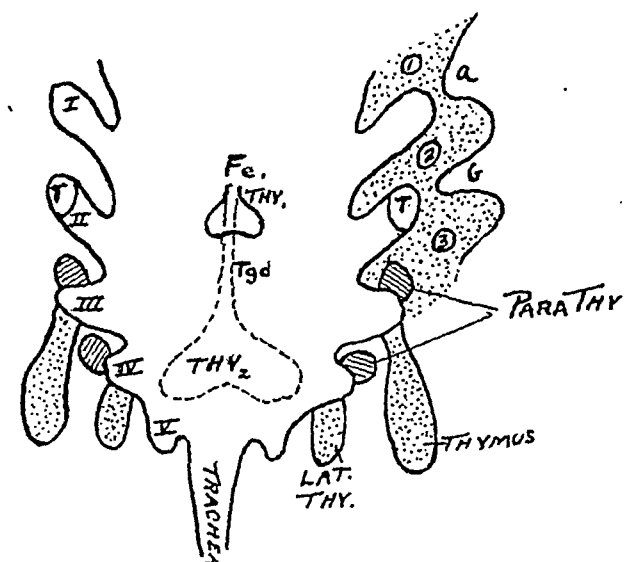


CHART I.—Diagram of pharynx of human embryo, showing the origins of the anlagen of the thymus, thyroid and parathyroid (epithelial bodies). *Thy₁*, earliest position of thyroid anlage; *Thy₂*, secondary position of thyroid anlage; *Tgd*, thyroglossal duct; *Fc*, foramen cecum; *Lat. Thy*, lateral thyroid anlagen; *Para Thy*, parathyroid bodies; *T*, tonsil; *I, II, III, IV, V*, pharyngeal pouches; *a, b*, first and second branchial grooves (gill clefts); *1, 2, 3*, first, second and third aortic arches in the cores of the branchial arches. (After Kohn.)

Histology. The epithelial cells of the parathyroid are of two chief types, the principal, and the oxyphil or acidophil cells.⁷

The principal cells are ovoid or polygonal with a clear cytoplasm and a large deeply staining spherical nucleus. The acidophil cells are less abundant and of similar shape, containing a small central spherical nucleus rich in chromatin and a deeply staining granular cytoplasm.

The cells are arranged in solid epithelial masses or cords and occasionally the cells surround a central lumen which is filled with an acidophil substance resembling colloid.

The connective tissue of the gland is variable, usually forming a thin distinct capsule and occasional trabeculae.

The blood supply of the parathyroid is very rich, indicating the activity of the gland.

Anatomy. The anatomic distribution of the glands varies to a great extent in the same species and to an even greater extent in different species.⁸ In man they are usually four in number, the superior pair lying close to the thyroid but not commonly within

the thyroid tissue, in the middle third of its posterior border approximately at the level of the cricoid cartilage.

The inferior pair ordinarily lies behind the lower third of the thyroid on a plane anterior to the recurrent laryngeal nerve and in close relationship to and usually anterior to the lower branches of the inferior thyroid artery.⁹ These are often found to be embedded in the thyroid tissue.

There have been found accessory parathyroids in various positions along the anlage route; sometimes embedded in the thymus or thyroid tissue. It is to the presence of these accessory glands that failure to produce fatal tetany in dogs after thyroparathyroidectomy has been ascribed.

In the light of recent work we are of the opinion that fatal tetany does not always occur in the usual time limits and that accessory parathyroids are not a common finding.

Surgical Significance. The importance of the parathyroid bodies was first determined some years ago by the results obtained when the thyroid gland was removed, and this is still the chief surgical significance. The occurrence of fatal tetany after total excision of the thyroid in some patients led to the discovery of these small bodies in the thyroid gland. They are now carefully preserved in operations for removal of a diseased thyroid. Cases have been reported, however, in which tetany occurred, although the parathyroids were apparently not touched. Such a case is here later reported in which the parathyroids were not thought to be disturbed although tetany occurred. This perhaps may be suggestive of a balance between the thyroid and the parathyroid.

The function of the parathyroids is unknown and although it is usually suspected that there is a relationship with other endocrine organs, what this relationship is, has yet to be determined. There is, however, a definite relationship between the parathyroids and calcium metabolism as evidenced by the fact that extirpation of the glands is usually followed by a distinct fall in blood calcium. Further evidence is given by the fact that the recently discovered active principle of the gland¹ when injected into normal animals causes a rise of blood calcium, and prevents the usual fall in blood calcium in parathyroidectomized dogs.

The occurrence of parathyroid tetany has been ascribed to lowered blood calcium alone, but evidence is now accumulating which may point to another explanation, the calcium change being an effect rather than a cause.^{1, 3, 15, 17, 26}

Another theory for the cause of tetany considered by Dragstedt² and Greenwald¹⁰ and others is that of intoxication. The prevention of tetany by bleeding and infusion of salt solution, and by intravenous calcium-free Ringer's solution¹⁵ is suggestive of a dilution of toxic products in the blood stream and consequent control of tetany. Search has been made for toxic substances in the blood of para-

thyroidectomized animals without success. Guanidin was suspected as a possible cause of intoxication,¹¹ but was not found consistently in increased amounts in the blood of parathyroidectomized animals.¹⁰ Guanidin poisoning is also not identical with parathyroid tetany.¹²

Parathyroid Tetany. When the parathyroid glands are completely removed from a dog, in about 90 per cent of cases,¹² there follows, after a symptom-free period of 2 to 5 days, the beginning symptoms of *tetania parathyreopriva*. These symptoms are first noticed as increased restlessness, loss of appetite and slight incoördination of gait, especially in the hind legs. Greenwald¹³ states that one of the first symptoms he notices is apparent headache, the dog rubbing its head against the sides of the cage and appreciating massage of the head.

Very soon after these symptoms have appeared one may feel fibrillary twitching of all of the muscles of the body, especially those of the hind legs and of the jaws. Later coarse tremors develop followed by increasing spastic contractions. The respirations are increased, salivation is profuse and the animal goes into long periods of spasticity with occasional clonic contractures of the leg muscles. If the attack of tetany lasts long enough to prevent respiratory movements, the animal dies. He may, however, have several attacks from which he recovers completely until a succeeding severe attack is fatal.

The occurrence of the tetany varies greatly in time of onset, severity and syndrome. It occurs with marked regularity, however, and various observers have stated that failure to produce fatal tetany after parathyroidectomy indicates technical failure to remove all the parathyroid tissue or indicates the presence of aberrant gland tissue.

It is a well-conceded fact that after parathyroidectomy there is a disturbance of calcium metabolism, so that there is a fall of blood calcium from a normal of 9 or 10 mg. per 100 cc. to 5 or 6 mg. per 100 cc. after 3 to 4 days. This observation suggests one of the theories of the origin and cause of parathyroid tetany. The adherents of the theory claim that the lowered calcium content of the blood is responsible for the fatal tetany. Further evidence is given by the increase in blood-calcium level following administration of the active principle of the parathyroid gland.¹ Greenwald¹⁴ has shown that calcium excretion is not increased after parathyroidectomy.

It is evident, however, that tetany can not be explained solely on a calcium deficiency basis, nor can the theory that tetany is due to an intoxication be accepted without further evidence.

Methods of Controlling and Preventing Tetany after Parathyroidectomy. Since Luckhardt and Rosenbloom¹⁵ and Dragstedt¹⁶ reported that tetany could be prevented in parathyroidectomized animals, several methods have been shown to be effective in preventing

death in these animals for periods of months to two years. None of these methods of controlling tetany are based upon any one principle. It seems to be true that if a parathyroidectomized animal is carried over the critical period, especially the second and third weeks after operation, by any one of these methods, it may live for long period of time with little or no treatment, only to be thrown into a severe or moderate attack by some apparent indirect influence, such as meat diet, estrus or pregnancy. It seems quite probable that in a large number of dogs undergoing parathyroidectomy, there would be a few that could withstand this critical period without fatal tetany. In the experience of men who have done this work, there are always a few dogs who do not show the characteristic symptoms in the usual 2 to 5 days. These have hitherto been considered failures in removing the parathyroid tissue or as indicating aberrant parathyroid glands. Very likely these dogs were imbued with whatever is necessary to withstand the critical period and live on just as the dogs who receive specific preoperative or postoperative treatment.

Luckhardt and Rosenbloom¹⁶ found that slow intravenous injections of Ringer's solution controlled and prevented tetany in parathyroidectomized dogs. Dragstedt and Peacock¹⁷ found that parathyroidectomized dogs placed on a meat-free diet did not develop tetany if administered lactose and milk in large quantities. Inonye¹⁸ corroborated this and found galactose also effective.

Oral administration of calcium lactate^{19, 20} and a combination of milk diet and intravenous injections of calcium chlorid²¹ were also effective.

Other methods of preventing tetany are oral administration of ammonium chlorid; ^{22, 23} magnesium chlorid; ²⁴ magnesium lactate²⁵ and strontium lactate.^{20, 26, 27}

Dragstedt²⁶ found that kaolin when administered by mouth kept parathyroidectomized dogs alive.

All of the above methods of preventing tetany are by means of postoperative therapeusis and indicate a control of the apparently abrupt change which occurs during the critical period, and which usually ends in fatal tetany. Some of these workers report that after a period of time varying from 6 to 8 weeks, the dogs became apparently normal, and were able to do without treatment and resume normal diets, even though the blood calcium remained at a low level. It is not unusual for these dogs to develop tetany late, brought on by pregnancy or lactation or by some unapparent cause. This also seems to hold true clinically in man. A woman was admitted to the New York Hospital with symptoms of gall-bladder disease. She had two years previously undergone a thyroidectomy for a toxic adenoma of the thyroid. Three days after this operation she developed signs of parathyroid deficiency, with one attack of tetany. She recovered completely and had no further

symptoms. The patient was again operated upon two years after the thyroidectomy and a gall bladder full of stones was removed. Three days postoperative she again suffered two attacks of quite severe tetany. She then recovered completely and has had no further symptoms.

Lately Brougher²⁸ has reported that postoperative administration of cod-liver oil and yeast delayed the onset of tetany and ameliorated its severity in parathyroidectomized dogs. He also reported that this treatment raised the blood calcium to normal. Buchbinder and Kern²⁹ have also reported that tetany is delayed after parathyroidectomy in jaundiced dogs.

The methods of preventing parathyroid tetany described above, all require postoperative treatment. In contrast to these is one requiring only preoperative treatment: Jones³ reported that the administration of cod-liver oil before the removal of the parathyroids is also effective in lengthening the lives of the parathyroidectomized dogs and in preventing tetany.

Our present experiments aim to repeat Jones' work, and, if successful, to study the calcium and cholesterol in the experimental animals and determine, if possible, their relationship.

Sweet,⁴ is of the opinion that calcium and cholesterol go hand in hand in metabolism and in his work on gall bladders³⁴ he found a definite change in the cholesterol content of the blood before and after cholecystectomy. If there is such a definite change in calcium metabolism in parathyroid deficiency, it is his opinion that there would also be a change in cholesterol metabolism, which if established might help to throw some light on the subject of the pathogenesis of parathyroid tetany. An example of the apparent association between these two substances is seen in acute nephrosis where there is found a disturbance of calcium and cholesterol in the blood, which is not explained entirely on the basis of retained blood substances. There may be a balance of some kind between calcium and cholesterol, such as might be explained by a mutually protective colloid mechanism. A disturbance of the balance might account for symptoms not explained by changed blood values above.

I have repeated Jones' work and found that cod-liver oil, when administered in doses of 20 to 50 cc. daily over a period of 2 to 3 weeks before operation prolongs the life of the thyroparathyroidectomized dog, delays fatal tetany and diminishes the severity of tetany when it does occur. The blood-calcium level drops as in untreated animals, reaching a lower level. Tetany was observed in 71 per cent of the treated dogs and it is not certain that it was absent in the other dogs. This work, therefore, does not confirm Jones' statement³ that this treatment prevents tetany. Greenwald³⁰ has also been unable to prevent tetany by the use of cod-liver oil as reported by Jones. All of the animals of this series died, one living 142 days after the operation.

Experimental Work. Dogs of any type were used as experimental animals, no selection being made as to age, size or sex. Five dogs were used as controls and 7 treated with cod-liver oil.

In all cases the thyroid was removed together with the parathyroid, care being taken to remove tissue immediately adjacent to the thyroid posteriorly. If the calcium level falls as usual² with the above technique, it seems logical to suppose all the parathyroid tissue removed, even without fatal tetany in 2 to 5 days. In only one case did the calcium level fail to fall as in the other dogs of this series, and this was taken to indicate failure of removal of all of the parathyroid tissue.

Several of the thyroids removed in this series were sectioned by Dr. José F. Nonidez, of the Department of Anatomy at Cornell University, and two parathyroids were found in each lobe. In all of these cases sectioned the parathyroids were embedded in the thyroid or closely associated with it under its capsule, so that complete extirpation of the thyroids in the majority of cases, and possibly all cases, assumes removal of all parathyroid tissue.

The control dogs were fed, *ad lib.*, the usual kennel diet, which consisted of bread, meat, table scraps and dog biscuit. No attempt was made to control the diet. It is quite evident that a dog cannot eat enough calcium or other material in a mixed diet such as this, to prevent the occurrence of tetany. The cod-liver-oil-treated dogs were also fed the usual kennel diet before and after operation, with the exception of Dogs 2 and 3 to whom a bread and milk diet was given after operation for one week. This seemed to have no effect on tetany appearance, so no further attempt was made to keep the dogs on milk or meat-free diet. Dog 1 ate this diet, including meat, daily, after operation until the day of occurrence of fatal tetany. All of the control and treated dogs recovered immediately after operation and showed no symptoms until the second or third day, when some refused food and became listless, and somewhat spastic. These symptoms increased slowly or rapidly, depending upon the number of days the animal lived.

The cod-liver oil was fed by stomach tube, daily. The dogs soon became accustomed to the tube and made no remonstrance to its introduction. Twenty cubic centimeters daily over a period of two weeks seemed to be adequate dosage and evidently optimal, for when the dosage was increased to 35 cc. for 42 days or 50 cc. for 30 days, no change in effect was noted and these dogs did not live as long as those treated with 20 cc. for 14 days. Dog 1, who lived the longest of the series, 142 days, received 20 cc. daily for 14 days before operation.

Blood samples were taken frequently and approximately at the same hour of the day, from the jugular vein. Calcium and cholesterol determinations were made on each sample.

From the accompanying chart (Chart II), it will be noted that

CHART II.—EFFECT OF COD-LIVER OIL ON THE TETANY OF PARATHYROIDECTOMIZED DOGS.

Controls.

No.	Sex.	Weight in kilos.	Age.	Treatment.	Diet.	Appearance of tetany, days after operation.	Died.	Lowest calcium, mg. per 100 cc.—day of occurrence.
19	F.	6.0	Old	None	Usual	31st and 32d	35th p.o. day	4.2; 10th p.o. day.
20	M.	6.0	Old	None	Usual	11th and 17th	23d p.o. day	5.4; 17th p.o. day.
12	M.	12.0	Old	None	Usual	Tremors on 7th and 10th	18th p.o. day	4.4; 16th p.o. day.
22	F.	2.0	Old	None	Usual	3d	4th p.o. day	8.7; 2d p.o. day.
9	M.	6.5	Old	None	Usual	2d	3d p.o. day	7.1; 1st p.o. day.

Cod-liver-oil Treated Dogs.

				Preoperative cod-liver oil.				
1	M.	3.0	Old	20 cc. daily, 2 weeks.	Usual	121st and 141st	142d p.o. day	5.4; 142d p.o. day.
3	F.	2.8	Young	20 cc. daily, 2 weeks.	Milk diet for 1 week p.o.	15th and 20th	32d p.o. day	4.1; 15th p.o. day.
10	M.	14.0	Old	35 cc. daily, 24 days	Usual	19th; died in tetany	22d p.o. day	4.4; 3d and 16th p.o. days.
2	M.	3.6	Young	20 cc. daily, 18 days	Milk diet for 1 week p.o.	None observed	17th p.o. day	5.4; 7th p.o. day.
11	F.	8.0	Young	35 cc. daily, 47 days	Usual	3d and 9th	11th p.o. day	6.0; 11th p.o. day.
15	M.	9.0	Young	50 cc. daily, 30 days	Usual	10th	13th p.o. day	6.0; 10th p.o. day.
17	F.	6.4	Young	50 cc. daily, 26 days	Usual	None observed	Killed 59th p.o. day	5.6; 10th p.o. day.

the treated animals lived longer than the control animals. The average length of life of the controls was 16.6 days and the average length of life of the treated animals was 42.3 days. It will be noted that all of the control dogs were "old," and that two, 19 and 20, lived 23 and 35 days. The calcium level fell as usual in these two dogs (see Charts VIII and IX). The symptoms were the usual ones seen in parathyroidectomized animals. Both animals died in tetany. This is taken to mean that these dogs were endowed with whatever material is necessary to delay fatal tetany.

Tetany appeared later in the treated animals, the average time of onset being at 35.6 days, while in the control dogs the average time of onset was at 10.8 days. Tetany was observed in all of the control animals and in all but two of the treated animals. In this respect only does this work differ from Jones in his report³ on the action of cod-liver oil on thyroparathyroidectomized dogs. Tetany was observed in 5 of the 7 treated dogs and the dogs were not observed closely enough to state that tetany did not occur in the other 2, but it is possible that they developed tetany as did those observed.

The tetany in the treated dogs was less severe than in the control dogs. In most cases the dogs became very emaciated after continued refusal of food and water, and this was borne out by autopsy.

Dog 1 lived the longest of this series, 142 days. This dog seemed exceptionally free from all symptoms, except for slight clumsiness of gait until the 121st postoperative day, when he suddenly developed tetany (Chart VI). He recovered from this in a few hours and was not observed to have further symptoms until the day of his second attack which proved fatal. This seems to indicate that an animal can live without parathyroid tissue and when carried over the critical period by some method, unexplained, will live indefinitely, but may at any time be subject to a return of tetany which may be fatal. The cause of this recurrence is unknown.

There is no evidence that other endocrine organs take over the function of the parathyroids when the glands are removed. All of these dogs were carefully autopsied and all of the endocrine organs of several animals were examined microscopically. The only persistent finding was a definite atrophy of the spleen to one-third to one-half its normal size. This may be explained by the fact that most of the dogs were greatly emaciated before death. In one dog (19) the pancreas was found to be granular, somewhat similar to a pancreas following ligation of the pancreatic ducts. On section, this proved to be a fibrosis of the gland with little normal tissue. One dog (1) showed a peculiar superficial ulceration of the gastric mucosa on the summits of the rugæ, with evidence of thrombosis of the vessels of the mucosa.

No changes were found in the thymus, suprarenals, testes, ovaries, or pituitary glands. All of the dogs who died slowly in emaciation

showed colons filled with impacted feces. No changes could be made out grossly in the liver or gall bladders.

Careful search for accessory or missed parathyroids was made in each dog and none found, although suspicious gross tissue was sectioned.

Blood Examination. As explained above, calcium and cholesterol determinations of the blood were made at intervals before and after operation. The author is greatly indebted to Dr. Nellis B. Foster for the blood chemistry work on this problem. This work was done in Dr. Foster's laboratory in The New York Hospital by his assistants. Calcium determinations were made according to Clark and Collip's modification of Tisdall's method³¹ and cholesterol determinations were done according to Bloor's modified method.³²

The "normal" calcium and cholesterol determinations were made on 12 normal dogs. These were all within close range of the average which was found to be 9.9 mg. of calcium per 100 cc. of serum and 160 mg. of cholesterol per 100 cc. of blood.

There was a quite definite relationship between the calcium and cholesterol findings in both the treated and control dogs. This is evidenced by the fact that in most cases when the calcium-level fell, the cholesterol level rose, and *vice versa*. This was most marked when symptoms of tetany appeared.

This is illustrated by the accompanying chart of Dog 11, who was treated with 35 cc. of cod-liver oil daily for 42 days before operation. At first, under the cod-liver oil treatment, there was a slight rise in the calcium and a coincident, more marked, cholesterol rise. Before operation there was a marked rise in calcium for the first time, the cholesterol decreasing at the same time. After operation there was a fall in cholesterol and a fall in calcium upon the first determination. But upon the first attack of tetany, the cholesterol rose sharply, although there was only a slight fall in calcium. At the time of onset of the second attack of tetany there was again the rise in cholesterol with a fall in calcium. This has been a common finding that in most cases of severe tremors and actual tetanic convulsive seizures, the cholesterol rose about as frequently as the calcium fell, and usually there was a greater proportionate change in cholesterol than in calcium. This is well illustrated by the accompanying charts. Dog 11 had no signs of tetany with a calcium of 8.5 mg. per 100 cc. while the cholesterol was at a low level. On the appearance of tetany the calcium was 8.2 mg. per 100 cc., but the cholesterol determination had risen sharply to 230 mg. per 100 cc. On the occurrence of the second attack, the cholesterol rose to a still higher level of 260 mg. per 100 cc. while the calcium fell to 6.1 mg. per 100 cc. On the following days before death, no tetany was evident although the calcium level continued to fall. Determinations of cholesterol taken at this time showed a fall.

In 13 determinations made on blood withdrawn during a con-

vulsion, the average calcium finding was 5.7 mg. per 100 cc., while the cholesterol finding was 222 mg. per 100 cc. The "normal" calcium was 9.9 and the "normal" cholesterol was 160, so that the rise in cholesterol seems to be as marked and significant as the fall in calcium.

Eight of the 13 cholesterol determinations made while the animal was in convulsions, gave the highest value obtained on the dog. Six of these 13 calcium determinations gave the lowest findings obtained. Many of the dogs were free from convulsions with the

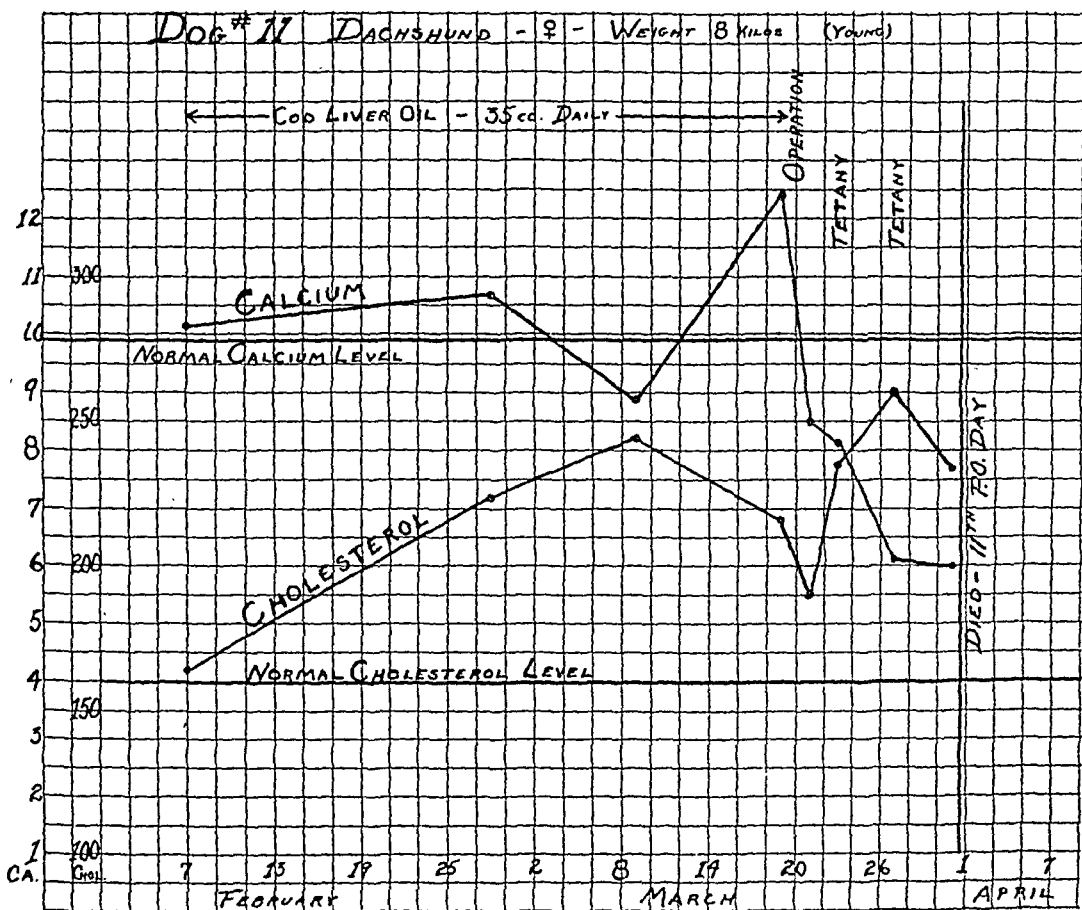


CHART III.

calcium at a "tetany" level, but in most cases the cholesterol was low. On the occurrence of tetany there would be little change in calcium but a definite change in cholesterol. In this series, throughout, there seems to be a relationship between the calcium and cholesterol performances. When the relationship was disturbed in some way, symptoms appeared.

There seems to be a more definite cholesterol change in the untreated dogs than in those treated with cod-liver oil. It was thought that perhaps the rise in blood cholesterol indicated a loss

of tissue cholesterol, and that the cholesterol content of cod-liver oil, which is 0.4 per cent, might be the explanation for the alleviation of tetany symptoms. In this connection, one dog was fed an egg diet containing 0.48 per cent cholesterol. After thyroparathyroidectomy this dog died in tetany just as the control dogs and no change in blood chemistry from the usual findings after operation was evident.

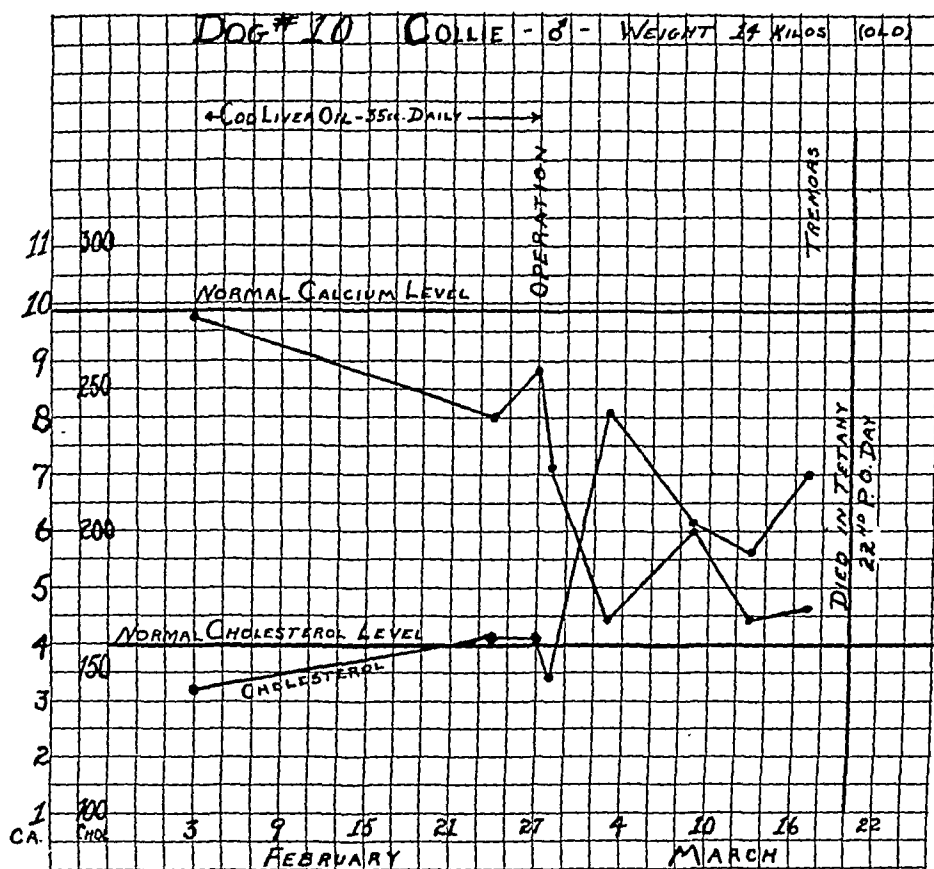


CHART IV.

McCarrison³⁵ states that the beneficial factor in cod-liver oil in the treatment of some of his thyroid patients may be due to its high iodine content. If this were true it might be inferred that cod-liver-oil treatment may be comparable to the administration of Lugol's solution. However, iodine is present in cod-liver oil in almost negligible quantities, 1 part in 5000. The iodine index and the iodine content are not to be confused.

Dog 10 further illustrates the relationship of calcium and cholesterol, although on the fifth day postoperative, when the calcium reached its lowest level and the cholesterol its highest level, no tetany appeared.

Dog 3, as shown on the chart, showed this condition quite clearly. On the day of first appearance of tremors, the cholesterol had his to its highest point and the calcium had fallen to its lowest point. Three days later, convulsions occurred but no blood samples were taken. The dog then recovered, apparently completely, and cholesterol taken 5 days after the convulsion showed a raised calcium and a very low cholesterol. Five days later a second tetanic attack occurred with the usual findings, that is, lowered calcium and increased cholesterol.

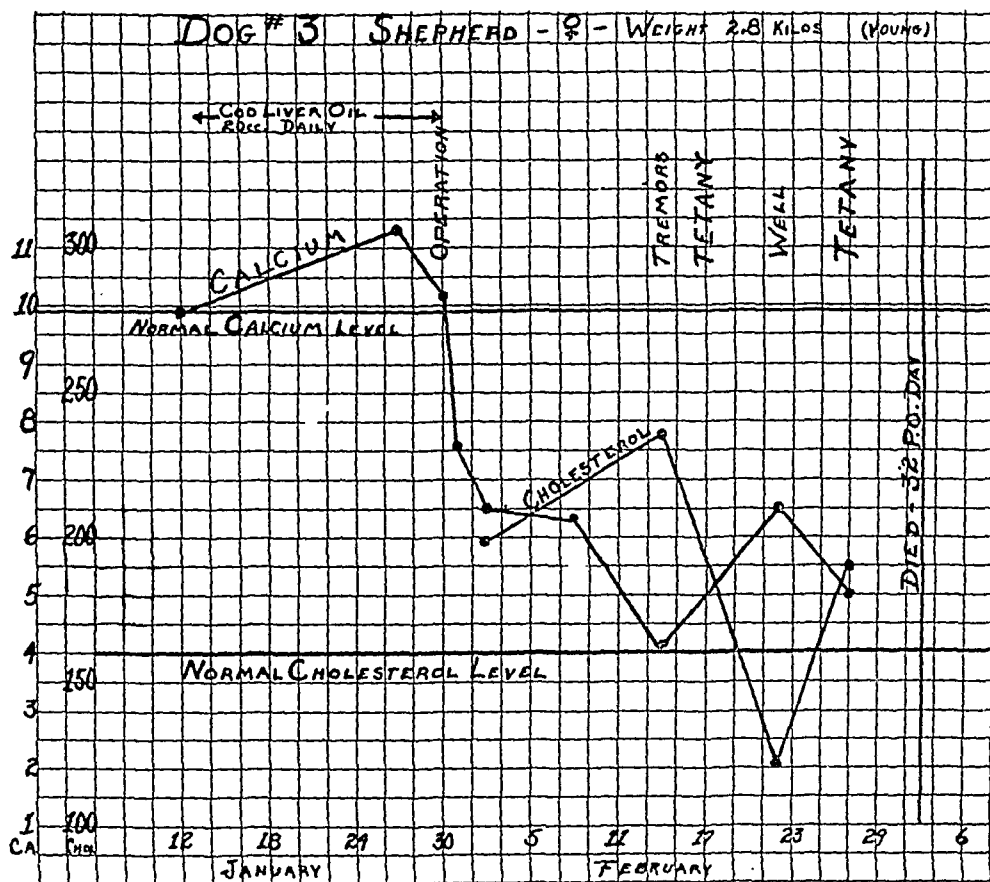


CHART V.

Dog 1 is especially interesting and bears out the finding of the importance of cholesterol in this experiment. This dog showed no symptoms whatever after operation, and calcium determinations taken at intervals showed a definitely lowered calcium and an insignificant rise in cholesterol. With the development of a sudden convulsive tetany, blood taken during the convulsion showed a slightly lowered calcium but a sharp and significant rise in cholesterol. The dog recovered thereafter, the cholesterol falling sharply. On the occasion of his second and fatal attack of tetany, the calcium value

very decided rise while the calcium varied only slightly. This occurrence on two occasions with a reversal of the cholesterol curve between attacks seems significant of some relationship between cholesterol metabolism and tetany.

The same relationship was found to hold true in the control dogs, with an even more marked cholesterol change than in the treated dogs,

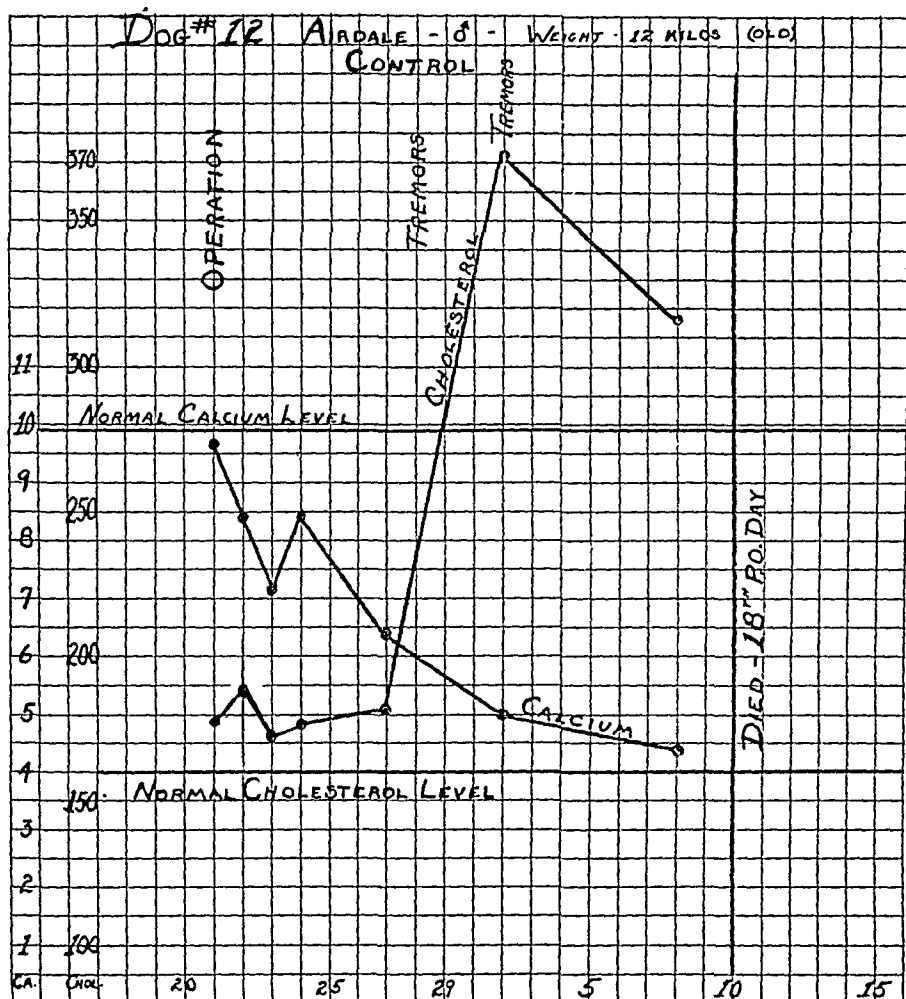


CHART VII.

Dog 12 showed tremors on the seventh and tenth days after operation, and examination of the blood showed a sharp rise in cholesterol. Later determinations during relief from symptoms showed a lowered cholesterol although the calcium level was still low.

Dog 19 bears out this theory more clearly. On the occasion of the lowest calcium value on the tenth postoperative day there were no symptoms, the cholesterol being at a low level. During the time the cholesterol hovered about the average normal, no tetany

Further evidence of the importance of cholesterol in this condition is shown in the chart of Dog 13, who was fed freshly ground thyroid material taken from Graves' disease patients at operation. In this dog the cholesterol rose as the calcium fell after continued feeding of the thyroids. After a short period of normal diet the curves returned to normal.

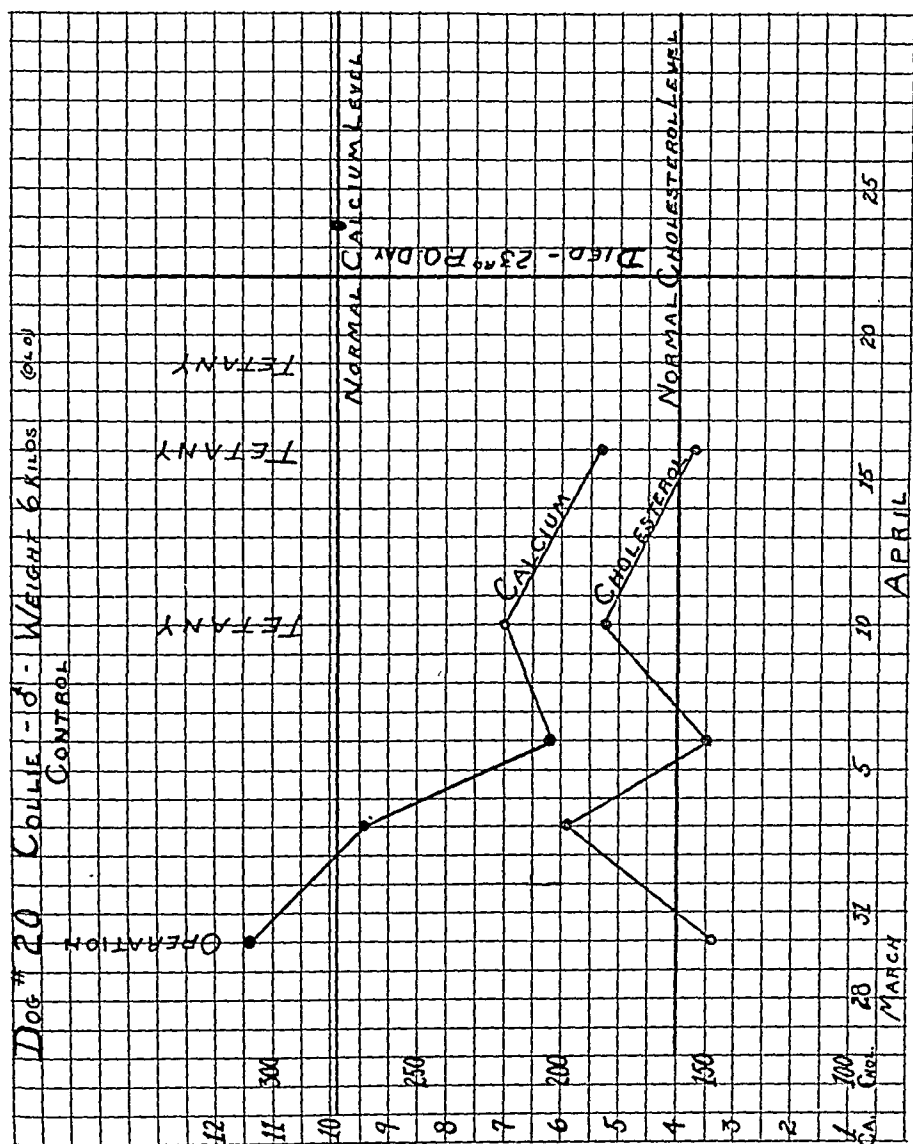


CHART IX.

It is interesting to note that Dog 1 lived with a definitely low blood calcium without symptoms for 142 days when tetany occurred. His skeleton was Roentgen-rayed at various times throughout the experiment and after death the bones were again Roentgen-rayed and examined, but no evidence of loss of calcium was found. He was also allowed to jump from a high table shortly before his death with no injury to the bones of his legs.

Ross³³ has recently reported that after prolonged low blood calcium the calcium content of the bone is diminished and that fractures of these bones heal slowly. Within the limits of these experi-

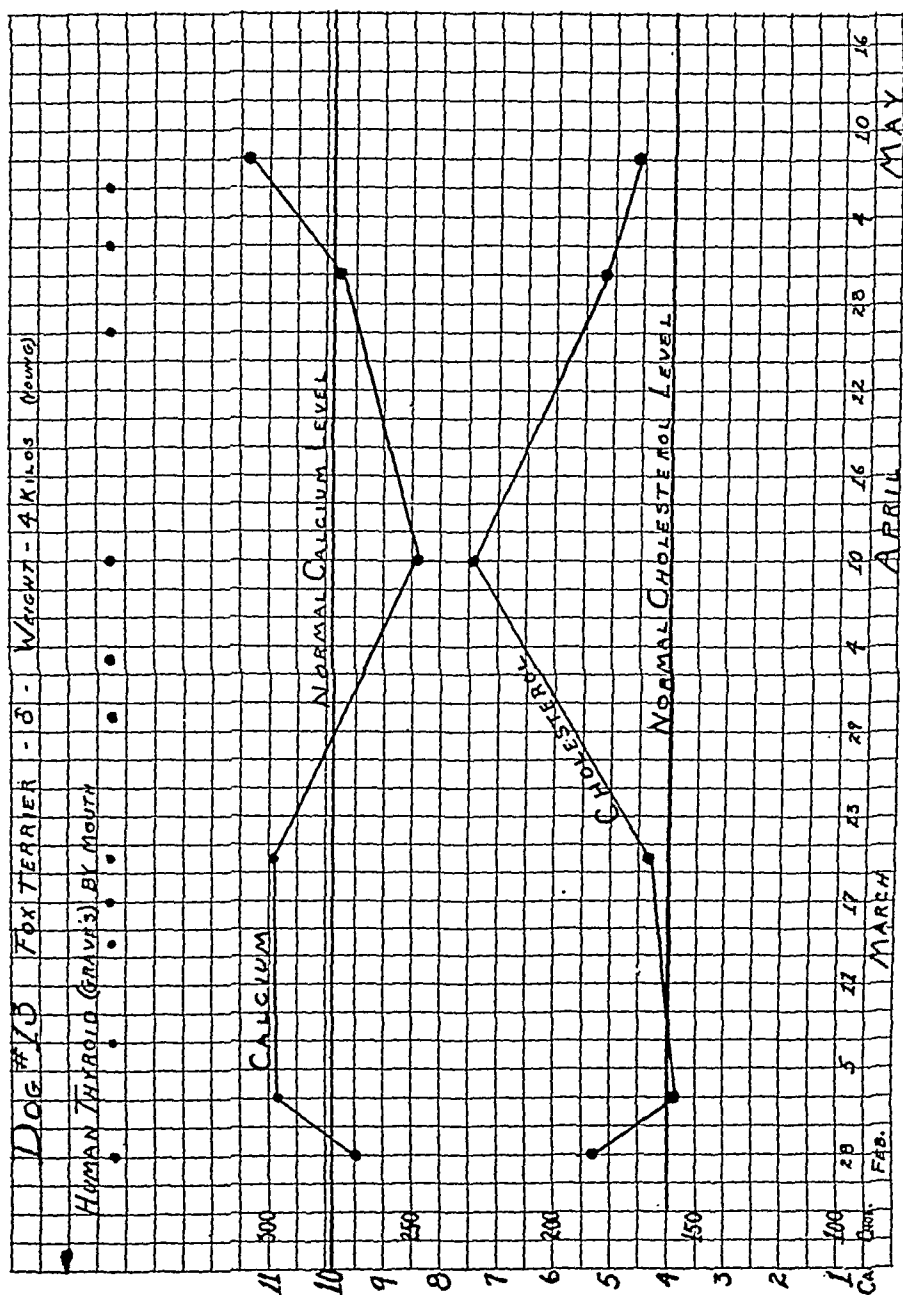


CHART X.

ments there was found no direct relationship between the prolonged low blood calcium and the calcium content of the bones.

From the above experiments it is here concluded that after thyro-parathyroidectomy in dogs there follows a rise in blood cholesterol which is about as consistent as the fall in blood calcium. The change

in cholesterol seems to be more marked than the change in calcium and seems to be more apparent in untreated dogs than in those having had cod-liver oil before operation.

Clinical Studies. In view of the findings of the experimental work, we have made calcium and cholesterol determinations on patients with diseased thyroids. Eleven patients were studied, all of whom had exophthalmic goiters or toxic adenomas of the thyroid.

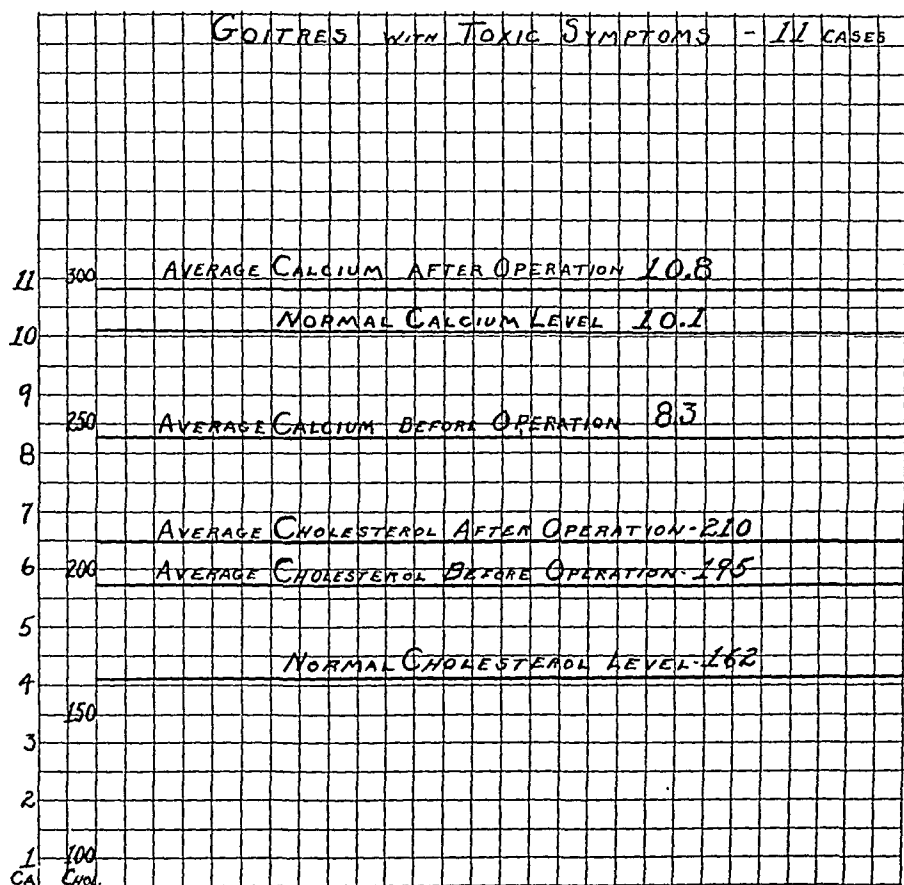


CHART XI.

"Normal" calcium and cholesterol levels were determined by the average of 10 normal individuals. The calcium average was 10.1 mg. per 100 cc. and the cholesterol average was 162 mg. per 100 cc.

In the study of these cases, we found that the calcium was consistently lowered in the untreated cases before operation. The more toxic the case, the more severe the symptoms, and the lower the calcium reading. The average calcium value on 11 untreated cases of toxic thyroid disease was 8.3 mg. per 100 cc. After operation all of the cases showed an increase in calcium in the blood. The average of the 11 cases after operation was 10.8 mg. per 100 cc.

In view of the low calcium findings in the severe cases of toxic thyroid disease, with an increase in calcium with the improvement of symptoms, it might be inferred that administration of calcium to these cases would be helpful in allaying symptoms.

Chart XII shows the effect of calcium feeding on a patient with exophthalmic goiter. Admitted with a basal metabolism of +48, the patient was treated by rest in bed with Lugol's solution, 80 minims daily. In one week the basal metabolism fell to +8 with a pro-

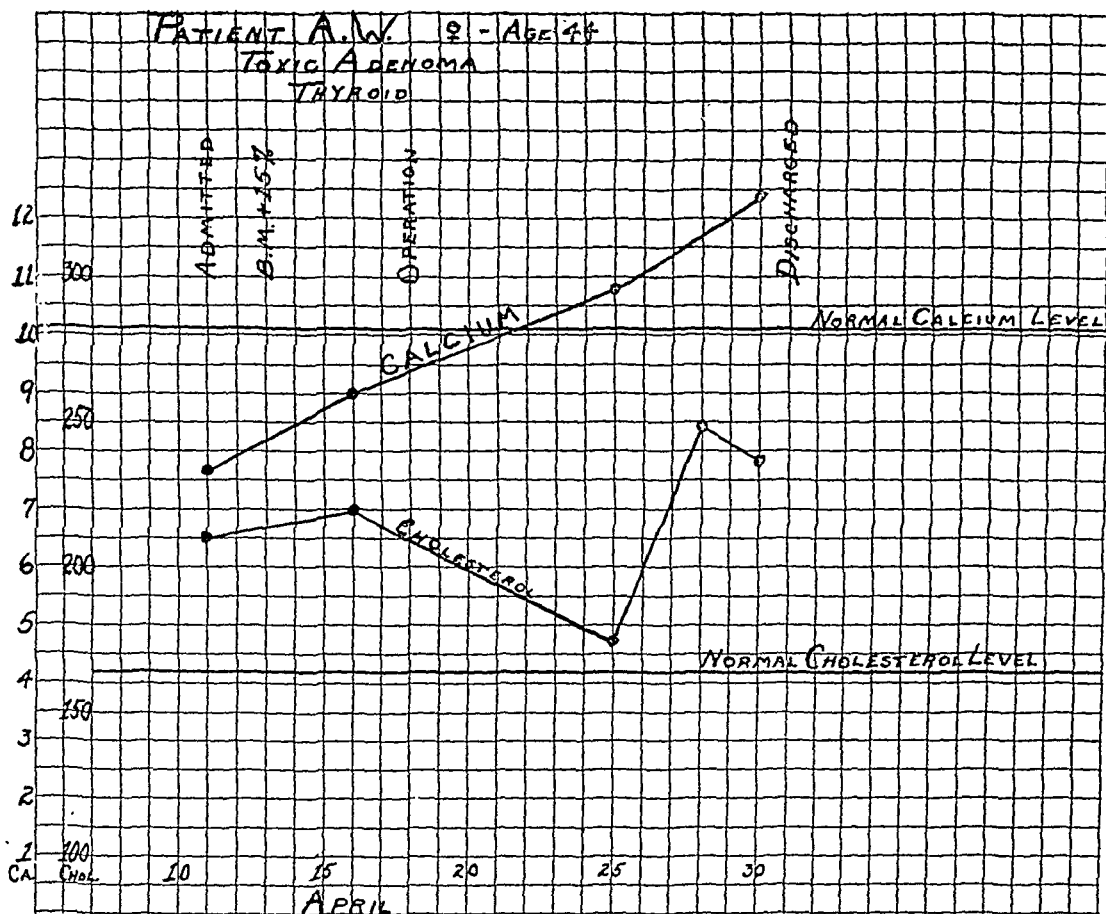


CHART XIII.

portionate alleviation of symptoms. At the end of this time calcium lactate was administered by mouth, 88 gr. daily. As shown in the chart in one week the basal metabolism rose to +58 and symptoms of hyperthyroidism became very much accentuated. The patient had remained in bed during the treatment, but the Lugol's treatment had been discontinued. The blood calcium rose to normal after the administration of calcium lactate by mouth. At the end of the week's experiment the calcium was discontinued and treatment with somewhat larger doses of Lugol's solution instituted.

Under this treatment, the symptoms disappeared quite readily and the basal metabolism rate fell in two weeks to +10. After discontinuance of the calcium treatment, the calcium again fell to a subnormal level but with improvement of symptoms it rose again to normal.

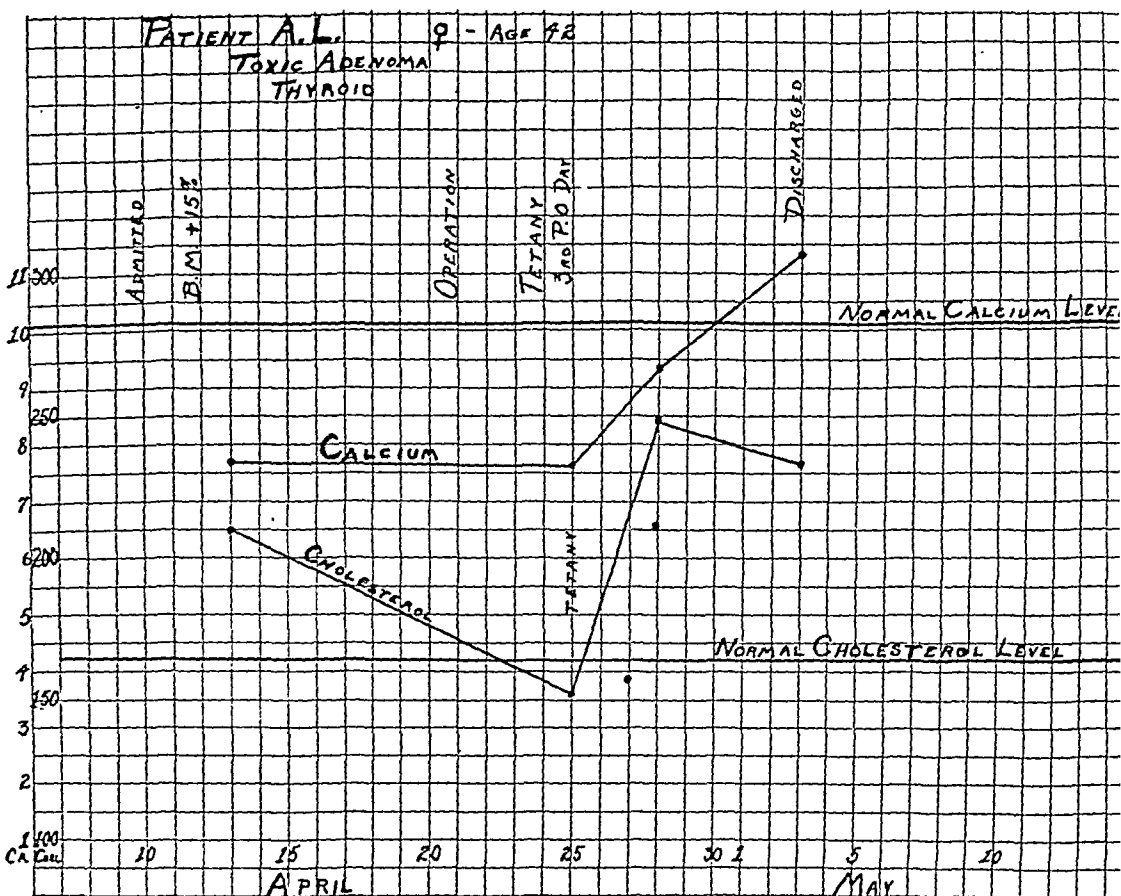


CHART XIV.

It is evident from the experience in this case that although the blood-calcium level is low in exophthalmic goiter, the administration of calcium aggravates the symptoms of the disease. We did not feel justified in repeating this experiment.

Chart XIII, a record of patient A. W., who was afflicted with a toxic adenoma of the thyroid, shows the usual picture of the blood calcium and cholesterol variations. As found in all of these cases the blood calcium was low, 7.6 mg. per 100 cc. Under treatment with rest in bed, the symptoms improved, and the calcium level rose somewhat before operation. After operation with an alleviation of symptoms the calcium rose as indicated to a level well above normal. As would be expected from the experimental work, the

cholesterol findings were high with a low blood calcium. After operation, as the calcium level continued to rise, the cholesterol, as expected. However, in both this case and the case of A. L., part XIV, there was a secondary rise in the cholesterol which is explained.

Patient A. L., also having a toxic adenoma of the thyroid, quite similar to the previous case, also had a low blood calcium, 7.7 mg. per 100 cc. on admission. The cholesterol finding was high as in the previous case.

At operation a subtotal resection of the thyroid was done, leaving the posterior portion of both lateral lobes of the thyroid. The parathyroids were not thought to be disturbed either directly or by interference with the blood supply. The patient did well after operation until the third day when she suddenly developed typical signs of tetania thyreopriva. There was a period of slight depression, the patient complaining of slight headache and occasional twitchings of the muscles of the hands and feet. There then developed a spastic condition of the hand, the flexor muscles alone being affected, so that the contraction assumed the characteristic position of Trousseau, the "accoucheurs hand," with a flexion of the index and middle finger and adduction of the thumb. The condition was bilateral, and of equal severity in both hands. The feet did not seem to be affected, although the feet assumed the tetanic position when pressure was made on the limb (Trousseau's phenomenon). Trousseau's symptom was also present at the time of onset of the attack.

The remarkable finding in this case was the undisturbed calcium level. A blood sample was taken at the onset of the attack before treatment was instituted and the calcium was found to be 7.7 mg. per 100 cc., practically the same determination as made two weeks before operation. This seemed to indicate that the parathyroids had not been disturbed. The cholesterol determination dropped to a normal level which was indicative also of the fact that the parathyroids had not been disturbed, since in the experimental work the cholesterol almost invariably rose after parathyroidectomy. These findings indicated a good prognosis.

Although it seemed certain that the condition would be temporary and recovery would probably be complete, it did not seem justifiable to delay treatment. Therefore, one dose of 40 units of Collip's parathormone was administered during the attack and an equal dose the following day. The attack subsided gradually and in a few hours the symptoms had completely disappeared. For two days thereafter, the patient was somewhat fearful that the symptoms would return, but convalesced rapidly with no further trouble. No further treatment was carried out and the patient was perfectly well when last seen, on November 1, 1928, having had no symptoms since leaving the hospital.

As shown on the chart the blood calcium rose to a point above normal after this attack and there was a secondary rise in the blood cholesterol as in the previous case.

This case seems to give evidence that there is some relationship between the parathyroid glands and the thyroid. When a diseased thyroid was removed, there were signs of parathyroid disturbance, as evidenced by the tetany, in the face of care in the anatomic preservation of the parathyroids and an undisturbed calcium level. As shown in the experimental work of this paper, the blood in a parathyroidectomized animal shows a fall in calcium and a rise in cholesterol. In this instance, tetany occurred without a fall in calcium and with a fall of cholesterol.

Summary. Action of Cod Liver Oil on Thyroparathyroidectomized Dogs. 1. An administration of cod-liver oil daily in doses of 20 cc. to 50 cc. over a period of from 14 to 30 days before operation, prolongs the lives of thyroparathyroidectomized dogs. Tetany is delayed and when it appears is diminished in severity. The calcium level falls as in control animals, and reaches a lower level than that of the control animals.

2. Thyroparathyroidectomized dogs may live for long periods of time if they are carried over the critical period of usual fatal tetany by some means such as cod-liver-oil treatment. Fatal tetany may occur at any time in "recovered" dogs.

Blood Calcium and Cholesterol in Thyroparathyroidectomized Dogs. 3. There is evidence that there is a relationship between the calcium and cholesterol content of the blood of thyroparathyroidectomized dogs. This perhaps indicates a relationship in the metabolism of calcium and cholesterol.

4. A fall in blood calcium is usually coincident with a rise in blood cholesterol, and *vice versa*.

5. In these experiments the occurrence of a rising cholesterol level in actual tetany was consistent with the occurrence of a decreasing calcium level.

Observations in Toxic Thyroid Disease. 6. In toxic thyroid disease, the blood calcium, in this series, was definitely lower than normal. After operation and alleviation of symptoms the calcium level rose consistently to a point above normal.

The blood cholesterol level was raised in these cases before operation, and rose only slightly after operation.

7. Administration of calcium lactate to one case of exophthalmic goiter with a low blood calcium was followed by aggravation of the symptoms of the disease.

8. Tetany occurred in one case of toxic thyroid disease, 3 days after operation. Anatomically the parathyroid glands were thought to be left intact, and the low blood calcium reading during tetany was approximately the same as before operation. The cholesterol level was also low during tetany.

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THE RELATIONSHIP BETWEEN SEDIMENTATION INDEX AND FIBRIN CONTENT IN RELATIVELY NORMAL INDIVIDUALS.

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Introduction. The sedimentation rate of blood cells has interested us for some time.^{1,2,3,4} As is well known, one explanation suggested for the rapid sedimentation rate in infections is the increased fibrinogen content. After reviewing previous work on this question we felt that a large series of cases should be studied with a statistical treatment of the data. This method of treating data is fairly new in blood chemistry studies, but we feel that it is to be extremely important in the future. In the course of the investigation, not only the relationship between fibrin content and sedimentation rate,

but also the relationship between fibrin content and age, and between sedimentation rate and age have received attention.

A brief review of previous work on the relationship between fibrin content and sedimentation rate will be given in chronologic order. Pfeiffer⁵ suggested such a relationship many years ago. Gram⁸ considered the fibrinogen content important in determining the sedimentation rate, through the agglutination of the corpuscles. Fahraeus⁹ concluded that an increased fibrinogen content was probably the most important cause for an increased sinking velocity.

Höber and Mond¹² found that fibrinogen decreased the negative charge on the cells, making the suspension less stable, and favoring a faster sedimentation rate. Linzenmeier¹³ believed likewise that the fibrinogen content was important in sedimentation. Wöhlisch¹⁴ considered that the speed of sedimentation was affected by the adsorption of fibrinogen on the surface of the red cells. Schindera¹⁶ held the opinion that the sedimentation rate depended upon the fibrinogen content. Holzweissig¹⁹ found that in general a parallel increase of fibrin content occurred with an increased speed of sedimentation. His series included 18 men and 82 women. Bruchsalser²⁰ found an increased fibrin content accompanying an increased rate of sedimentation in pregnancy. In none of these studies did we find the question of the relationship between fibrin content and sedimentation rate answered to our satisfaction.

A review of the work on the fibrin content of the blood will be given. It will be observed that practically no attention has been directed to the relationship between fibrin content and age. Lewinski⁶ found that the fibrin content in healthy men and women ranged from 0.27 to 0.48 per cent. Whipple⁷ found that the fibrin content in man varied between 0.3 and 0.6 per cent, with an average of 0.5 per cent. Gram⁸ found an average of 0.27 per cent of fibrin in the plasma of 25 men and 0.29 per cent in 25 women. McLester¹⁰ found a range of 250 to 400 mg., with an average of 0.333 per cent for 15 normal individuals, and an average of 0.829 per cent for 20 sepsis patients. The fibrin content seemed fairly constant in health. Gram,¹¹ in further studies, found that the fibrin content does not vary in the course of the day, nor in relation to meals. He found it increased in tuberculosis, averaging 0.62 per cent in 21 cases.

Foster,¹⁵ in a study of 42 cases, including men from 6 to 63 years of age and women from 16 to 63 years, found an average of 0.332 per cent for men and 0.344 per cent for women. The fibrin content did not parallel the white count. Weltmann¹⁷ found a variation of 0.13 to 0.26 per cent in normal individuals. McLester¹⁸ found a wide variation in fibrin in disease. Bruchsalser²⁰ found a higher content in women than in men, the normal range being from 64 to 125 mg.

Chandler²¹ gives an excellent review of the work on fibrin content

of the blood plasma, discussing the various methods that have been used. In his work he first used the Wu colorimetric method.²² He states that he found a white precipitate developing in the flasks before the time occurred for matching in the colorimeter. (We had the same difficulty at one time, but learned from Drs. Fahr and Swanson that the phenol reagent must be kept in a cool dark place, and made up freshly each month. Observing these precautions eliminated the difficulty. We experienced another difficulty at one time. The tyrosin standard seemed to lose its original strength. We found a growth, apparently a mold, not only in the tyrosin, but also in the reserve bottle of $\frac{N}{10}$ hydrochloric acid. The whole was discarded, and a new solution of $\frac{N}{10}$ acid made up. No further difficulty was experienced, either in the acid or tyrosin standard.) Chandler's difficulty with the precipitate led him to determine the nitrogen in the fibrin by the Folin microkjeldahl method. In a series of ten normal individuals he found a range of 0.226 to 0.388 per cent, and in 4 cases during menstruation he found a range of 0.125 to 0.304 per cent. He made a fairly extensive study of pregnancy cases, as well.

The question of the relationship between the sedimentation index and age has not been answered by previous work. Consequently, the present piece of work was undertaken to gain information on these three questions: The relationship between fibrin content and sedimentation rate; the relationship between fibrin content and age; the relationship between sedimentation index and age. Our series is great enough to permit statistical treatment of the data, which we believe to be essential in blood chemistry studies. Incidentally, interesting sex differences appeared in the course of the work.

Results. This series was carried out on individuals as nearly normal as could be conveniently found at the various ages.²⁵ The 7 to 17-year group was composed entirely of children attending Lymanhurst School. They were undernourished, but able to attend school regularly. They came from families in rather humble circumstances. They were under observation at Lymanhurst because of previous contact with open cases of tuberculosis.

The 18 to 28-year group consisted of students attending the University of Minnesota. Because of the difference in these first two groups it seemed advisable to base our studies on groups 7 to 17, 18 to 28, 29 to 39 years, and so forth, rather than on decades. Most of the students in the 18 to 28-year group were in very good health. The 29 to 39-year group contained several medical students, several faculty members, and some patients attending the University Dispensary. The patients were derived from various clinics, such as neurology, dermatology and internal medicine. They were all up and about, and engaged in regular work of some sort.

The 40 to 50-year group included some faculty members, some

physicians, and patients, comparable to those in the 29 to 39-year group. The 51 to 61-year group included physicians, some dispensary patients and some individuals of Parkview Sanatorium. These were chronic cases, some suffering from partial paralysis, some from decompensated hearts, some from arthritis, and so forth. They were no longer able to be self-supporting. The 62 to 72-year group included Parkview patients, and dispensary patients, mostly from the ear and heart clinics. The dispensary patients were up and about, of course, as were some of the Parkview patients. Those above 72 were of the same type. While the material used in these studies has not been normal, it may be described as relatively normal, since most of the individuals were up and about, and working, and were free from acute infection.

The blood was drawn by venepuncture, usually about two hours after the last meal. The sedimentation rate was determined by the Cutler graphic method,²³ using 0.5 cc. of potassium oxalate (4.4 per cent) instead of citrate. Readings were taken at 15-, 30-, 45- and 60-minute intervals, except in one additional group, in which readings were taken at frequent intervals over a 19-hour period. The fibrin was determined in duplicate on plasma from the same sample as used for the sedimentation rate. The Wu colorimetric method²² was used, with slight modification, observing the precautions mentioned in the introduction.

1. Entire Group of Each Sex. The series included 200 women and 213 men, ranging in age from 7 to 94 years. The average sedimentation index (one hour reading) for women was 9.54 ± 0.25 mm.; the range was from 1 to 28 mm. The average index for men was 8.14 ± 0.34 mm., with a range of 1 to 31 mm. The difference between the sexes is 1.39 ± 0.42 mm. This is 3.3 times as large as its probable error. Similar differentiation exists in tuberculosis patients.²⁴ Our results substantiate in a quantitative way the findings of earlier investigators.

The average fibrin content for women was 0.3045 ± 0.0027 gm. per 100 cc. of plasma. The range was from 0.20 to 0.55 gm. The average fibrin content for men was 0.3253 ± 0.0039 gm., the range being from 0.20 to 0.80 gm. The difference between the sexes is 0.0208 ± 0.0047 gm. Being 4.4 times as large as its probable error, it is significant. Similar differentiation was found in tuberculous patients.²⁴ We differ from other investigators in finding the average fibrin content lower in women than in men.

The usual statistical methods have been employed. For advice in connection with the use of these methods we are greatly indebted to Prof. J. Arthur Harris. A study of the relationship between fibrin content and sedimentation index gave a correlation coefficient, r_{FS} , of 0.533 ± 0.034 for the women. (F = grams of fibrin per 100 cc. of plasma and S = sedimentation index in millimeters.)

The correlation is significant, since it is 15.7 times as large as its probable error.

The linear regression equation, calculated from the means, standard deviations, and correlation coefficient is $F = 0.2492 + 0.0058S$, where, as above, F = grams of fibrin per 100 cc. of plasma and S = the sedimentation index in millimeters. The empirical mean fibrin contents as ordinates are plotted against the indices in Chart I.

The correlation coefficient, r_{FS} , for the men was 0.749 ± 0.020 . This is 37.4 times as large as its probable error. The linear regression equation is $F = 0.2547 + 0.0087S$. The empirical mean fibrin values as ordinates are plotted against the indices in Chart I.

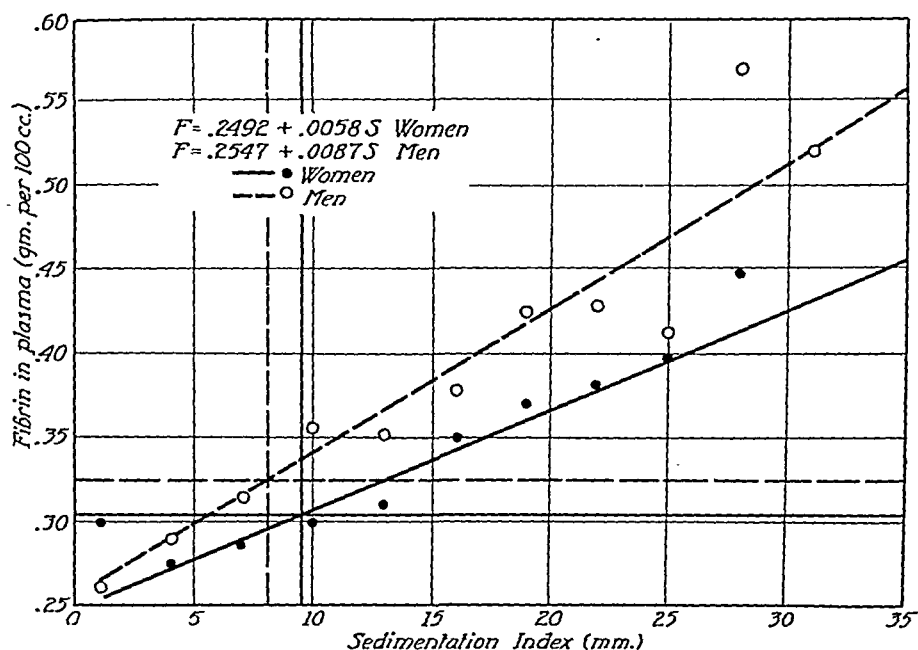


CHART I.—Relatively normal individuals, relationship between fibrin content and sedimentation index.

The difference between the correlation coefficients for the two sexes is 0.216 ± 0.039 . We are unable to account for the significantly greater correlation in men.

2. Investigation of Women of Different Ages. The foregoing results were found on the entire group of women. The group will now be divided into 6 subgroups, according to age. The subgroups will include women from 7 to 17, 18 to 28, 29 to 39, 40 to 50, 51 to 61 and 62 to 72 years of age. The results for each subgroup are presented in Table I.

It will be observed in Table I that the index tends to increase with age. The fibrin first decreases, then increases. The correlation coefficient is significant in every group.

TABLE I.—RELATIVELY NORMAL WOMEN. AVERAGE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT OF EACH SUBGROUP AND THE ENTIRE GROUP.

No.	Age.	Index, mm.		Fibrin, gm. per 100 cc. of plasma.		Corr. coeff., † FS = P.E.	r. P.E.r.
		Average.	Range.	Average.	Range.		
24 . .	7-17	6.50	4-16	0.3021	0.25-0.35	0.374 ± 0.118	3.1
75 . .	18-28	7.76	1-16	0.2840	0.20-0.45	0.322 ± 0.070	4.6
27 . .	29-39	7.56	1-19	0.2815	0.20-0.40	0.320 ± 0.116	2.7
25 . .	40-50	12.40	4-22	0.3240	0.25-0.55	0.577 ± 0.090	6.4
25 . .	51-61	13.72	4-28	0.3420	0.25-0.50	0.644 ± 0.079	8.1
18 . .	62-72	11.83	4-22	0.3278	0.25-0.45	0.373 ± 0.137	2.7
200 . .	7-94	9.53	1-28	0.3045	0.20-0.55	0.533 ± 0.034	15.7

The deviations of the index, fibrin content and correlation coefficient for the subgroups, classified according to age, from the comparable constants for the group as a whole are shown in Table II. These differences are taken (constant for subgroup) less (constant for entire group), in order to give signs which will show whether the constants for the subgroups are larger or smaller than those for the entire group.

TABLE II.—DEVIATIONS OF THE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT FOR THE SUBGROUPS, FROM THE COMPARABLE CONSTANTS FOR THE GROUP AS A WHOLE. THE ENTIRE GROUP CONSTANTS ARE THE SUBTRAHENDS.

Age.	Deviation of index.	Deviation of fibrin content.	Deviation of correl. coeff.
7-17	-3.03	-0.0024	-0.159
18-28	-1.77	-0.0205	-0.211
29-39	-1.97	-0.0230	-0.213
40-50	+2.87	+0.0195	+0.044
51-61	+4.19	+0.0375	+0.111
62-72	+2.30	+0.0233	-0.160

The first three subgroups have a smaller index, the last three a larger index than the entire group. The fibrin contents are lower in the first three subgroups and higher in the last three, than in the entire group. The correlation coefficient is smaller in all the subgroups except the 40 to 50- and 51 to 61-year groups, than in the group as a whole.

An additional group of 56 women, mostly between 18 and 30 years of age, was studied to determine if the one-hour reading gave as reliable a picture of the relationship between the fibrin content and the sedimentation rate as readings at other intervals. Table III presents for each time interval the average index, the correlation

coefficient and the deviation of the latter from the coefficient for the 1-hour reading. These differences are taken (coefficient for given interval) less (coefficient for 1-hour reading), in order to give signs which will show whether the coefficients for the various time intervals are larger or smaller than that for the 1-hour reading.

TABLE III.—FIFTY-SIX NORMAL WOMEN. THE AMOUNT OF SEDIMENTATION, THE CORRELATION COEFFICIENT, r_{FS} , AND THE DEVIATION OF THIS COEFFICIENT FROM THE 1-HOUR COEFFICIENT. (THE AVERAGE FIBRIN CONTENT FOR THIS GROUP WAS 0.2732 ± 0.0044 GM. PER 100 CC. OF PLASMA.)

Time.	Sed., mm.	Coeff. of corr., $r_{FS} \pm P.E.$	r	Deviation of correl. coeff.	Diff.
			P.E.r.		P.E. diff.
15 min.	1.32	0.462 ± 0.071	6.5	-0.115 ± 0.092	1.20
30 "	4.27	0.562 ± 0.062	9.0	-0.015 ± 0.086	0.20
45 "	7.00	0.623 ± 0.055	11.3	$+0.046 \pm 0.082$	0.50
1 hr.	9.36	0.577 ± 0.060	9.6		
1½ hrs.	12.14	0.573 ± 0.060	9.5	-0.004 ± 0.084	0.05
2 "	14.12	0.589 ± 0.059	9.9	$+0.012 \pm 0.084$	0.10
4 "	18.03	0.582 ± 0.059	9.8	$+0.005 \pm 0.084$	0.06
6 "	19.43	0.530 ± 0.065	8.2	-0.045 ± 0.088	0.50
8 "	20.08	0.521 ± 0.065	8.0	-0.056 ± 0.088	0.60
10 "	20.55	0.510 ± 0.066	7.7	-0.067 ± 0.089	0.70
19 "	21.36	0.462 ± 0.071	6.5	-0.115 ± 0.092	1.20

The correlation coefficient is significantly greater than its probable error at every time interval studied. Thus the readings at any time interval, corrected to a standard time interval, may be used to determine the relationship between fibrin content and sedimentation rate. The deviations of the coefficient at the given time interval from the 1-hour coefficient are insignificant.

A study of the relationship between sedimentation index and age gave a coefficient, r_{AS} , of 0.486 ± 0.036 for the women. (A = age in years and S = sedimentation index in millimeters.) The coefficient is 13.5 times as large as its probable error. The linear regression equation is $S = 4.52 + 0.14 A$, where, as above S = sedimentation index in millimeters, and A = age in years. The empirical mean indices as ordinates are plotted against the age in Chart 2.

The correlation coefficient, r_{AF} , between fibrin content and age was 0.355 ± 0.042 for the women. The coefficient is 8.4 times as large as its probable error. The linear regression equation is $F = 0.2646 + 0.0011 A$, where F = grams of fibrin per 100 cc. of plasma and A = age in years. The empirical mean fibrin contents as ordinates are plotted against the age in Chart 3.

3. Investigation of Men of Different Ages. The results for the group of men as a whole have been given. The subgroups, according

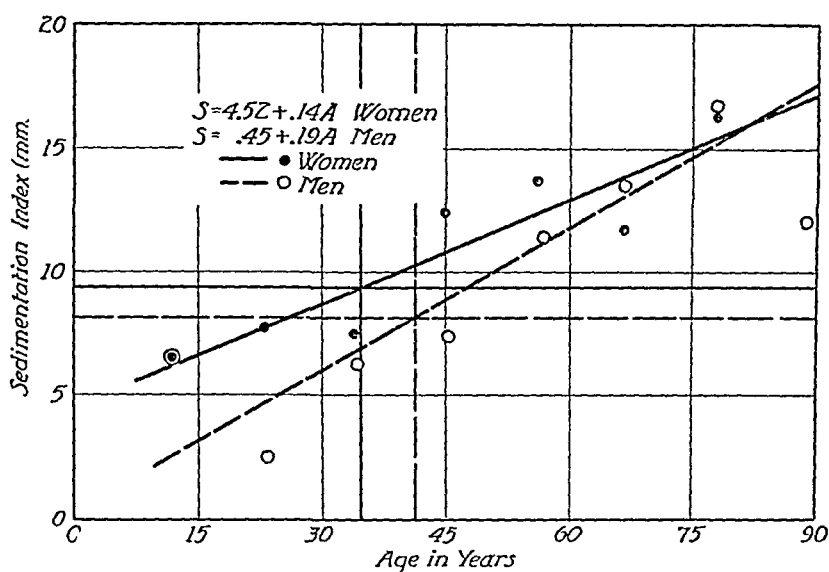


CHART II.—Relationship between sedimentation index and age.

to age, include men from 7 to 17, 18 to 28, 29 to 39, 40 to 50, 51 to 61, 62 to 72 and 73 to 83 years of age. The results for each subgroup are presented in Table IV.

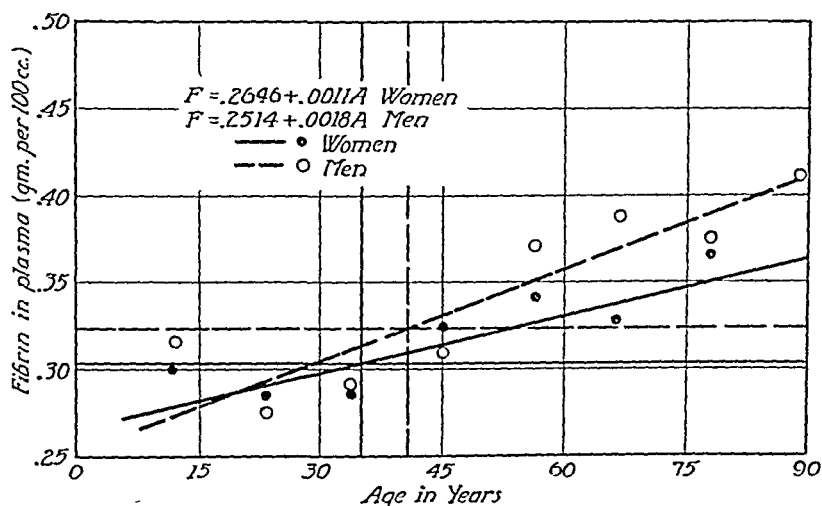


CHART III.—Relationship between fibrin content and age.

As seen in Table IV, the index increases with age, except in the 18- to 28-year group. The fibrin content first decreases, then increases. The correlation coefficient is significant in every group with the exception of the 18 to 28-year group.

TABLE IV.—RELATIVELY NORMAL MEN. AVERAGE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT OF EACH SUBGROUP AND THE ENTIRE GROUP.

No.	Age.	Index, mm.		Fibrin, gm. per 100 cc. of plasma.		Corr. coeff., $r_{FS \pm P.E.}$	r P.E.r.
		Average.	Range.	Average.	Range.		
30 . .	7-17	6.60	1-16	0.3183	0.20-0.40	0.497 ± 0.093	5.3
53 . .	18-28	2.53	1- 7	0.2707	0.20-0.40	0.167 ± 0.090	1.8
26 . .	29-39	6.08	1-28	0.2904	0.20-0.50	0.769 ± 0.054	14.2
27 . .	40-50	7.33	1-28	0.3093	0.25-0.55	0.757 ± 0.055	13.7
26 . .	51-61	11.50	4-25	0.3731	0.25-0.55	0.747 ± 0.058	12.8
31 . .	62-72	13.68	1-31	0.3903	0.20-0.80	0.746 ± 0.054	13.8
17 . .	73-83	16.88	4-31	0.3794	0.30-0.50	0.512 ± 0.120	4.3
213 . .	7-94	8.14	1-31	0.3253	0.20-0.80	0.749 ± 0.020	37.4

The deviations of the index, fibrin content and correlation coefficient for the subgroups, classified according to age, from the comparable constants for the group as a whole are as shown in Table V. These differences are taken (constant for subgroup) less (constant for entire group), in order to give signs which will show whether the constants for the subgroup are larger or smaller than those for the entire group.

TABLE V.—DEVIATIONS OF THE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT FOR THE SUBGROUPS, FROM THE COMPARABLE CONSTANTS FOR THE GROUP AS A WHOLE.

Age.	Deviation of index.	Deviation of fibrin content.	Deviation of correl. coeff.
7-17	-1.54	-0.0070	-0.252
18-28	-5.61	-0.0546	-0.582
29-39	-2.06	-0.0349	+0.020
40-50	-0.81	-0.0168	+0.008
51-61	+3.36	+0.0478	-0.002
62-72	+5.54	+0.0650	-0.003
73-83	+8.74	+0.0541	-0.237

The first four subgroups have a smaller index and a lower fibrin content than the group as a whole. The last three subgroups have a larger index and a higher fibrin content than the group as a whole. The correlation is smaller in all the subgroups except the 29 to 39- and 40 to 50-year groups, than in the group as a whole.

A study of the relationship between sedimentation index and age gave a coefficient, r_{AS} , of 0.554 ± 0.032 for the men. (S = sedimentation index in millimeters and A = age in years.) The coefficient is 17.3 times as large as its probable error. The linear regression equation is $S = 0.45 + 0.19 A$. The empirical mean sedimentation indices as ordinates are plotted against the age in Chart 2.

The correlation coefficient, r_{AF} , between fibrin content and age was 0.460 ± 0.036 for the men. This is 12.8 times as large as its probable error. The linear regression equation is $F = 0.2514 \pm 0.0018 A$, where F = grams of fibrin per 100 cc. of plasma and A = age in years. The empirical mean fibrin contents as ordinates plotted against the age in Chart 3.

We hope that future work will include reinvestigation of the origin of fibrinogen, the mechanism of its increase in infections and the cause for the more rapid sedimentation of blood cells in various diseases. Although we have found a significant correlation between fibrin content and sedimentation rate in all cases but one, we do not consider the relationship a causal one. The chief reason for this point of view lies in the fact that women have a statistically significantly faster sedimentation rate than men, with a lower fibrin content.

Summary. 1. The sedimentation index (Cutler graphic method) in a series of 200 relatively normal women averaged 9.54 ± 0.25 mm.; in 213 relatively normal men it averaged 8.14 ± 0.34 mm. The difference between the two sexes is 1.39 ± 0.42 , which is statistically significant, as in tuberculous patients.²⁴

2. The fibrin content (Wu colorimetric method) for the women averaged 0.3045 ± 0.0027 gm. per 100 cc. of plasma. The average for the men was 0.3253 ± 0.0039 gm. The difference between the two sexes is 0.0208 ± 0.0047 gm., which is statistically significant. Similar sex differentiation exists in tuberculous men and women.²⁴

3. The correlation coefficient, r_{FS} , between fibrin content and sedimentation index is 0.533 ± 0.034 for the women and 0.749 ± 0.020 for the men. Both show a significant relationship between fibrin and sedimentation rate. We have no explanation for the significantly greater correlation in the men.

4. The average index increased from 6.50 ± 0.44 mm. in the 7 to 17-year group to 11.83 ± 0.86 mm. in the 62 to 72-year group of relatively normal women. The difference between the highest and lowest age groups is 5.33 ± 0.97 mm. The difference is statistically significant. The coefficient of correlation (r_{AS}) between sedimentation index and age is 0.485 ± 0.036 .

In the men the average index increased from 6.60 ± 0.40 mm. in the 7 to 17-year group to 13.68 ± 1.0 mm. in the 62 to 72-year group. The difference between these age groups is 7.08 ± 1.1 mm. The coefficient of correlation (r_{AS}) between sedimentation index and age is 0.553 ± 0.032 . Both sexes show a significant relationship between sedimentation index and age.

5. The average fibrin content increased from 0.3021 ± 0.0037 gm. in the 7 to 17-year group to 0.3278 ± 0.0085 gm. in the 62 to 72-year group of women. The difference between these groups is $0.0257 \pm$

0.0093 gm. The coefficient of correlation, r_{AF} , between fibrin and age in women is 0.355 ± 0.042 .

In men the average fibrin content increased from 0.3183 ± 0.0063 gm. in the 7 to 17-year group to 0.3903 ± 0.0145 gm. in the 62 to 72-year group. The difference between these groups is 0.072 ± 0.016 gm. The coefficient of correlation, r_{AF} , is 0.459 ± 0.035 .

Both sexes show a significant relationship between fibrin content and age.

6. In both sexes a significant correlation between fibrin content and sedimentation index exists, not only in the groups as a whole, but also in the subgroups, with the exception of the 18 to 28-year group of men.

7. In an additional group of 56 women significant correlation was found between the fibrin content and the amount of sedimentation at 15, 30 and 45 minutes, 1, $1\frac{1}{2}$, 2, 4, 6, 8, 10 and 19 hours. There was excellent agreement between the coefficients so found.

Conclusions. From the above results we draw the following conclusions:

1. The sedimentation rate of red cells is faster in women than it is in men.

2. The fibrin content is lower in women than it is in men.

3. As the fibrin content increases, the sedimentation rate becomes more rapid. The relationship is more constant in men than it is in women. Although this relationship between fibrin content and sedimentation rate is evident in both sexes, we are not convinced that it is a causal one. Our chief reason for this is the fact that women have a lower fibrin content, but a faster sedimentation rate than men. The question must receive further study.

4. The sedimentation rate increases with age in both men and women.

5. The fibrin content increases with age in both men and women.

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INCREASE IN BLOOD SUGAR FOLLOWING THE INGESTION OF GLYCEROL.

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VOEGLIN, Dunn and Thompson have reported observations indicating that intraperitoneal injections of glycerol can prevent and relieve hypoglycemic shock in albino rats.¹ In this animal, the curative effect, which requires only about ten minutes, approximates the effect produced by the injection of a similar amount of glucose. According to these authors, glycerol will also relieve the hypoglycemic symptoms following the injection of insulin in rabbits, although in this animal larger doses are required—8 to 12 gm. per kilo of body weight.

These authors suggest that the antagonistic action of glycerol on insulin is due to a conversion of glycerol into glucose. In order to test this possibility, they have determined the effect of glycerol on the blood sugar concentration of fasted rabbits.² In these experiments they found that glycerol given to fasted rabbits per os or intraperitoneally produces a hyperglycemia of considerable extent and duration. They have concluded that this indicates a conversion of glycerol into sugar.

TABLE I.—INFLUENCE OF 100 GM. GLYCEROL ON THE BLOOD SUGAR IN CASES OF DIABETES.

Case.	Blood sugar, Mg. per cent.						Urine, sugar.			
	Sex.	Age.	Fast- ing.	1 hr.	2 hr.	3 hr.	Fasting.	1 hr.	2 hr.	3 hr.
4, N. N.	M.	57	90	..	150	..	Neg.	Neg.	
9, M. K.	F.	57	190	..	230	250	Neg.	2%	2%
10, A. T.	M.	66	160	..	190	190	Neg.	Neg.	Neg.
11, P. C.	F.	58	125	..	130	140	Neg.	Neg.	Neg.
12, P. P.	F.	45	220	..	220	200	Neg.	Neg.	Neg.
13, E. R.	F.	39	170	..	230	270	Neg.	Neg.	Neg.
15, R. T.	M.	53	260	..	350	330	95 cc.— 1%	100 cc.— 2.2%	75 cc.— 1.4%
16, E. T.	F.	52	210	..	240	..	Neg.	Neg.	
17, M. S.	F.	50	170	..	195	175	Neg.	Neg.	Neg.
18, E. R.	F.	57	115	160	Neg.	Neg.		
20, B. C.	F.	64	250	..	360	300	5 cc.— 0.5%	100 cc.— 0.5%	100 cc.— 0.5%
22, I.	F.	47	85	..	130	130	Neg.		
23, H. G.	F.	55	220	..	210	..	15 cc.— 0.5%	400 cc.— 2%	Neg.
24, B. S.	F.	46	105	..	160	..	Neg.	Neg.	
27, D. B.	F.	40	200	..	200	190	Neg.	Neg.	Neg.
28, A. R.	F.	52	140	..	180	160	Neg.	Neg.	Neg.
29, S.	M.	50	100	..	145	125	Neg.	Neg.	Neg.
30, C.	F.	47	230	..	230	300	50 cc.— 0.5%	150 cc.— tr.	200 cc.— Neg.
31, A. O'C.	F.	58	190	..	170	..	25 cc.—1%	50 cc.—tr.	
32, S.	M.	38	95	..	130	..				
33, J. L.	F.	55	110	..	180	..	Neg.	0.5%	
35, D. K.	F.	65	160	..	210	230	Neg.	Neg.	Neg.
36, C. M.	F.	58	160	..	300	200	Neg.	Neg.	1 plus
37, J. C.	M.	54	200	..	180	200	Neg.	Neg.	Neg.
38, L. C.	F.	60	190	..	220	200	Neg.	Neg.	Neg.
39, F. S.	F.	62	85	..	170	84	Neg.	Neg.	Neg.
41, M. C.	F.	65	170	..	180	..	Faint trace	Faint trace	
42, M. H.	M.	29	290	310	75 cc.— 5%	55 cc.— 7.1%		
43, H. S.	F.	55	134	166	Neg.	Neg.		
44, P. G.	M.	62	110	..	160	..	Neg.		Neg.	
46, A. B.	F.	54	140	..	160	..	Trace	Neg.	
47, J. R.	M.	63	180	..	180	180	Neg.	Neg.	Neg.
49, E. M'C.	M.	67	125	..	165	170	Trace	Trace	Neg.
50, H. R.	M.	63	105	..	140	140	Neg.	Neg.	Neg.
55, D. K.	M.	63	290	..	308	266	1 plus	1 plus	1 plus
56, J. G.	F.	53	130	..	121	160	Neg.	Neg.	Neg.
57, V. C.	F.	35	180	..	225	204	Neg.	1 plus	1 plus
58, F.	F.	58	155	..	230	190	Neg.	1 plus	1 plus
59, M. S.	M.	45	110	..	115	..	Neg.	Neg.	Neg.
60, D. K.	F.	50	110	..	125	125	Neg.	Neg.	Neg.

TABLE II.—INFLUENCE OF 100 GM. GLYCEROL ON THE BLOOD SUGAR IN CASES OF DOUBTFUL DIABETES.

Case.	Blood sugar, Mg. per cent.						Urine, sugar.			
	Sex.	Age.	Fast- ing.	1 hr.	2 hr.	3 hr.	Fasting.	1 hr.	2 hr.	3 hr.
14, S. G.	F.	42	120	..	115	110	Neg.	..	Neg.	Neg.
19, S. D.	F.	50	100	116	Neg.	Neg.		
21, M. C.	M.	44	105	130	Neg.	Neg.		
25, A. S.	F.	48	75	..	76	..	Neg.	..	Neg.	
34, S. A.	F.	62	92	..	110	..	Neg.	..	Neg.	
40, E. N.	F.	58	135	..	135	..	Trace	..	Faint trace	
53, M. P.	F.	32	95	..	85	..	Neg.			

TABLE III.—INFLUENCE OF 100 GM. GLYCEROL ON THE BLOOD SUGAR IN NONDIABETICS.

Case.	Blood sugar, Mg. per cent.						Urine, sugar.			
	Sex.	Age.	Fast- ing.	1 hr.	2 hr.	3 hr.	Fast- ing.	1 hr.	2 hr.	3 hr.
1. Neuralgia . .	F.	41	100	112	Neg.	Neg.	..	Neg.
2. Arthritis . .	M.	43	75	..	75	60	Neg.	..	Neg.	Neg.
3. Arthritis . .	M.	43	95	..	95	75	Neg.	..	Neg.	Neg.
5. Nephritis . .	F.	17	114	..	95	90	Neg.	..	Neg.	
6. Arthritis . .	F.	50	72	104	Neg.	Neg.		
7. Arthritis . .	F.	47	140	175	Neg.	Neg.		
8. Hypertension	F.	48	85	95	Neg.	Neg.		
26. Hypertension	F.	53	70	..	65	..	Neg.	..	Neg.	
45. Sciatica . .	M.	56	100	95	Neg.	Neg.		
48. Hypertension	F.	65	120	..	90	..	Neg.	..	Neg.	
51. Hypertension	F.	48	88	..	76	..	Neg.	..	Neg.	
52. Post operative gall bladder	F.	59	100	..	160	..	Neg.	..	Neg.	
54. Exophthalmic goiter . .	M.	33	95	..	120	..	Neg.	..	Neg.	

TABLE IV.—SHOWING THAT NONFERMENTABLE SUGAR IS NOT INFLUENCED BY THE RISE IN BLOOD SUGAR CAUSED BY THE INGESTION OF GLYCEROL AND THAT THIS INCREASE IS FERMENTED BY YEAST.

Case.	Blood sugar, Mg. per cent.			Nonfermentable "rest reduction," Mg. per cent.		
	Fasting.	2 hr.	3 hr.	Fasting.	2 hr.	3 hr.
4. Diabetes	90	150	...	17	20	36
16. Diabetes	210	240	17	
17. Diabetes	170	175	175	33	40	
32. Diabetes	95	130	...	20	24	
46. Diabetes	140	160	...	11	10	
51. Hypertension	88	76	...	14	20	
52. Postoperative gall bladder .	100	160	...	14	22	
53. Diabetes (?)	95	85	...	10	8	
54. Exophthalmic goiter	95	120	...	10	14	

In our observations we have determined the effect of glycerol on the blood sugar of 60 patients. Of these, 40 were definitely diabetic, 7 were doubtful diabetics, 4 were cases of hypertension, 4 of arthritis, 1 of nephritis (mild, with normal blood chemistry), 1 of exophthalmic goiter, 2 of neuralgia, and 1 had gall stones removed. We classify as doubtful diabetics those cases who while under our observation had no sugar in the urine, had a normal fasting blood sugar, some

giving a negative blood-sugar curve after the ingestion of 100 gm. glucose, but with a history of glycosuria previous to our observation.

Method of Procedure. The patient was given on an empty stomach at least ten hours after last meal, 100 gm. glycerol in 250 to 300 cc. of water. At the beginning the glycerol was divided into two doses and given at a fifteen-minute interval, but later the whole amount was given in one dose. Blood was withdrawn immediately before and then again in two and three hours after the administration of glycerol. In some cases blood was withdrawn before and then only once, one or two hours after the glycerol. In each case the urine passed by the patient just before the withdrawal of each sample of blood, was tested for sugar.

Fermentation by yeast is considered the most accurate method for the determination of sugar, and modern investigators are increasingly using the fermentation process for the determination of blood sugar. The term "sugar" as commonly applied to the blood, includes all the substances determined by the reduction method. These include glucose, unknown sugars and some nitrogenous products in the tungstic acid blood filtrates. Yeast fermentation removes all the glucose and other unknown sugars but leaves the nitrogenous products. These are designated as nonfermentable sugars (rest reduction). This nonfermentable sugar is, according to Folin and Svedberg, independent of the original sugar level of the blood and amounts to about 20 mg. per cent when Folin-Wu reagent is used. According to these authors, the yeast works just as expeditiously in tungstic acid filtrate as in pure sugar solution.³ In 9 of our series of cases, the tungstic acid blood filtrate was fermented with yeast in order to determine whether the increase in reducing substances caused by the ingestion of glycerol, is removable by fermentation. If this increase is removable by fermentation, then it must be due to glucose and other unknown sugars, and not to the nitrogenous products in the filtrate. There are no known practical chemical means of differentiating glucose from other unknown sugars in the blood, and from the chemical point of view, such substances as glyceric aldehyde, which may be produced from glycerol within the body, cannot be excluded. The figures given in Table IV are those of the nonfermentable fraction of reducing substances (rest reduction) after the others have been removed by yeast. These are also the uncorrected figures, that is, without subtracting the "blank" which is gotten by suspending yeast in water, and is equivalent to from 3 to 5 mg. per cent.

Clinical Reaction. In general, there was little if any reaction following the ingestion of glycerol. In no instance were there any gastrointestinal disturbances reported such as vomiting or diarrhea. Only 5 patients complained of any discomfort, which was usually a throbbing headache or dizziness and in one case was associated with marked erythema of the face. The erythema in the last case was

followed by some scaling of the skin. The headache in some of the cases might well have been due to lack of food. Of the 5 patients who had any unpleasant reaction only one, Case VI, gave a rise in the reducing substances of the blood. It is reasonable to assume that the discomfort of the patient had no effect on this rise.

Discussion. In the laboratory, glycerol may be converted into hexose. It is believed that in this process, dioxyacetone and glyceric aldehyde are formed and that two molecules of either of these may be polymerized to form a hexose molecule. When this process occurs in the animal body, the hexose formed is glucose.⁴ Voegtlin and his collaborators have shown that the rise in blood sugar following the administration of glycerol to rabbits, is not due to a concentration of the blood. On the other hand, they could not exclude the possibility that the increase in blood sugar might be due to glyceric aldehyde produced from glycerol within the body.

From an analysis of our case reports, it will be seen that the very marked rises in blood sugar occurred in the more progressive case of diabetes. Twenty-seven of the 40 cases of diabetes (67.5 per cent) show an increase of 20 or more mg., while only one of seven doubtful cases shows an increase of 25 mg. Four cases of hypertension gave no increase whatsoever. Of the 4 cases of arthritis, 2 show no rise, 1 had a fasting blood sugar of 140 and should, therefore, be considered as a potential diabetic. Only Case VI shows a rise of 32 mg. one hour after the glycerol. One case of sciatica gave no increase, while a case of neuralgia gave an increase of only 12 mg. Case 52 (recent gall bladder operation) does indeed show an increase of 60 mg. two hours after the glycerol. The well known association of diabetes with infections of the biliary tract suggests the possibility that this case is a potential diabetic. One case of nephritis gave no increase and the case of exophthalmic goiter gave an increase of 25 mg.

If the rise in blood sugar is due to glyceric aldehyde, one would find it difficult to explain the difference in behavior between the diabetic and the nondiabetic person. The hyperglycemia curve in a diabetic after the ingestion of glycerol resembles, in its extent as well as in its duration, the curve obtained after the ingestion of glucose. In Case 9, the fasting blood sugar was 190 mg. and the urine was negative. Two hours after the ingestion of glycerol the blood sugar was 230 mg. and the urine contained 2 per cent of sugar. Three hours after the blood sugar was 250 mg. and the urine showed 2 per cent of sugar. Cases 20, 23, 33, 36 and 42 show that part of glycerol is excreted as sugar in the urine.

These observations, we believe, favor the conclusion of Voegtlin and others, namely, that the increase in blood sugar following the ingestion of glycerol, is due to the extra presence of glucose.

Summary. Glycerol given to a human being on an empty stomach, will produce a hyperglycemia. The extent of the hyper-

glycemia is in direct ratio to the disturbance of carbohydrate metabolism of the particular individual. In the more progressive cases of diabetes, the glycerol may produce a glycosuria as well as a hyperglycemia. These facts warrant the conclusion that in the human body, glycerol is converted into glucose.

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THE PLACE OF FUNGI IN MODERN MEDICINE.*

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IN the above title the significant words are two, "fungi" and "modern." I shall at once proceed to discuss fungus disease as a whole, and toward the end of the paper shall indicate which developments are modern, or at least promise to lead to results which were not possible in the past.

More and more, and year by year, the average medical man is realizing that fungi at least occasionally play a part in human disease. The pathologist informs him over the cadaver that his case of vertebral osteomyelitis was caused by actinomyces. In the laboratory, he tells him that his case of meningitis was caused by a yeast, and then the dermatologist advises him that the omnipresent, bothersome cracked toes or even an eczema on the dorsa of his feet were caused by fungi and that the infection passed under the euphonious name of dermatophytosis. He is now quite aware that there is smoke in the air and that, after that, there must of course be some real fire at the bottom of it. This much he readily concedes, but he needs and deserves more. The question is how much fire and how to get at it.

Too, the general medical man is quite aware of the obstacles in the way of making diagnoses of fungus infections, besides the elimination of fungus factors as possibilities in a differential diagnosis, and that the hazards stretch not only through the clinical

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domain but extend also beyond the frontier into laboratory territory. Indeed, I feel that the short-comings are much more serious in the laboratory than in the clinic; most of the fungus infections are of the subacute or chronic type which as a class are the more difficult to diagnose, which bear more or less close resemblance to tuberculosis, and which the laboratory man ought to shed more light upon. Most laboratory men will honestly confess that they have little or no training in mycology and that they approach such problems with a great deal of hesitation and unwillingness, just as the average practitioner confesses that he has not mastered dermatology and otology to the extent that he has the other specialties.

The explanation for these delinquencies is not hard to find. Both in the clinical and in the laboratory realms, fungus cases occur far less commonly than the bacterial ones; indeed, it is certain that they will never attain the importance of the bacterial infections. Fungi are far less important than bacteria—at least as we know them now. In the second place, mycologic technique and classifications are radically different from bacterial; if anything, they are more involved than the bacterial. This would mean that the laboratory man, to become quite competent, would be obliged to master yet another biologic field. Already he is sorely beset in attempting to keep pace with such diversified fields as modern serology and biochemistry in addition to older established morbid anatomic, parasitologic, chemical and bacteriologic sections. Pathologists just at present are in great demand; many hospitals are on the outlook at the present moment for good men. The result is that in the face of such immediate crying needs something has to go by the board, and mycology is the phase which has had to suffer.

The remedy, likewise, is clear. Not that every pathologist should be expected to at once assume courses in mycology. This is not necessary in the present state of affairs. What is quite feasible, however, and entirely justified, is the establishment of at least a few laboratories in different sections of the United States with staff pathologists who have taken courses and conducted intensive studies in mycology and can render assistance to the clinician when called upon to assist him in his mycologic problems. To come yet closer to the point, actual ways and means, what we need is a liaison between the first-class clinician and first-class mycologist, the former supplying data and material in a consistent, uniform, systematic way, and the pathologist working up the materials and advising with the clinician. Neither clinician nor pathologist can work alone, they must go hand in hand. Beginnings of this sort should be made in our larger, including tuberculosis, centers. I hear the clinicians inquiring how they can investigate their cases of pulmonary disease and detect the fraction of them at least that are not of tuberculous causation.

The considerations in mycology are not purely academic; indeed,

there is a very practical aspect to the situation. For a long time, it has been known that iodine and the iodids are specific in many fungus infections, and fungus infection extends over a long range of organisms, all the way from the delicate streptothrices, which are so closely related to the tubercle bacillus, through the yeasts and fungi imperfecti to such specialized members as the aspergilli, for instance. The Roentgen rays, likewise, have achieved brilliant results in many fungus infections. With the advent of modern intravenous therapy the therapeutic field has opened up yet more widely, and now that it has been demonstrated that iodine can be administered intravenously in such amazing doses the urgent necessity of identifying fungus cases and of giving patients the benefit of specific fungus treatment is all the more emphasized.

The foregoing applies to conditions in the United States. It also applies to most other parts of the world. But France, Italy, and some of the South American countries with Latin affinities constitute outstanding exceptions. In these countries there is an enormous literature on mycologic subjects; these countries are far ahead of the English- and German-speaking ones.

Incidence. After these introductory remarks, let me pass to a consideration of the frequency, as we know it today, with which the various organic systems are likely to be found infected by fungi. It will be observed, as we go along, that frequently it is not so much the fungus affection but the recognition that is rare.

Speaking in general, fungi have a predilection for the same orders of body tissue as the tubercle bacillus. Thus, fungi are rarely, if ever, found in heart or skeletal muscles, or in the pancreas. They are best known on the skin, in the lungs, bones, and after that scatteringly in other organs, such as brain, kidney, spleen, liver, and so forth. Most of the infections are local, confined to the skin, lungs, or bone, as the case may be. Notoriously, however, blastomycosis, sporotrichosis, coccidioidal granuloma, and actinomycosis may become generalized.

In the succeeding paragraphs the attempt will not, could not, be made to indicate the full extent to which the different systems become parasitized by fungi, but simply to offer outstanding illustrations and type cases which will serve to bring home to the physician at large concrete examples of what may be expected to crop out in his experience from time to time; that is, to what extent he must be alert to pick out the occasional instances of fungus infection.

Generalized Cases. In order to prevent tiresome repetition under each of the different systems to follow, let us recall that actinomycosis, blastomycosis, sporotrichosis and coccidioidal granuloma notoriously become generalized, and that practically no organ or tissue may escape secondary involvement. In actinomycosis, it is generally known that the primary focus is usually in bone. In blastomycosis and sporotrichosis, it is most commonly in the skin.

In coccidioidal granuloma, there is an undercurrent of feeling that it is frequently a primary pulmonary affection; but from the case reports to date it would appear that the skin is the primary site in most cases. Other fungus species may give rise to secondary lesions, but those just mentioned are the most important.

In the sections to follow, instances of primary involvement will be selected for the most part.

Respiratory System. To enumerate all of the fungi which have been claimed as pathogens in this system would be meaningless. Suffice it to say that practically all of the fungus orders are represented, extending from the thread organisms all the way up to such highly organized ones as the aspergilli and the mucors. The latter are indeed the more spectacular and attractive cases; but from the practical standpoint the streptothrices and blastomycetes are the important members. Monilias are responsible for many cases of bronchitis and asthma, as has been brought out by Castellani¹ and Steinfeld.² Nathan³ has remarked that patients are commonly sent to a sanatorium where in time they acquire tuberculosis, so that the course of the case ultimately confirmed the erroneous diagnosis.

Both American and foreign authorities are agreed that in most cases fungus infections of the lungs are clinically indistinguishable from tuberculosis and that the only hope of identifying the fungus cases is through laboratory means. This is an important point to keep in mind. Mendelson,⁴ in reporting cases of pulmonary mycosis and spirochetosis, even went as far as to insist that tuberculosis can only be ruled out by animal inoculation; this is of particular importance to the laboratory man and finds expression because many of the streptothrices are acid-fast, may assume a beaded form, and thus closely resemble tubercle bacilli in stained preparations. Mendelson⁵ also appeals to physicians, especially in the tropics, to rely more on laboratory tests and less on physical signs. Thus, in 100 pulmonary cases which he reported, 5 per cent were caused by fungi, 23 per cent by spirochetes, and the remainder were tuberculous; tubercle bacilli were identified only in 10 per cent of the latter. The importance of accurate diagnosis comes to us with special force when one recalls that the iodid therapy which is contraindicated in open pulmonary tuberculosis is sometimes a specific in the fungus cases.

A further point of tremendous importance to the laboratory man, and one which occasions much puzzlement, is the determination of pathogenicity. From such material as sputum, indeed even normal mouths, it is only to be expected that various forms of fungi will be isolated. Indeed, there is a proper skepticism as to the pathogenicity of most of the species for which such a property has been claimed. There can be no doubt that the list of valid pathogens should be much shorter; but, of course, it will never be possible

to state just what proportion of species is pathogenic and which commensal. We can say, however, that where the attempt has been seriously made it has been possible to satisfy all of the postulates of Koch. Magalhaes,⁶ for instance, has proven *Oidium braziliensi* as a pathogen by injection into guinea-pigs; he also reproduced the human disease in a monkey by exhibiting the fungus by inhalation. All organs showed fungus, especially the lungs. He stated that the symptoms in his cases were like those of tuberculosis except that there were no night sweats.

To cite a concrete example of pulmonary mycosis, Callender and Coupal⁷ have described a case of nocardiosis secondary to inhalation of a chicken vertebra into the lung. It would be possible to multiply the reports of interesting cases which attest the definiteness and importance of fungus infections of the bronchopulmonic apparatus (Lapham,⁸ Nicaud,⁹ Hamman¹⁰), but we must pass to the other systems.

The Digestive Tract. This certainly ranks next in order of importance. Probably the best known illustration of a digestive tract mycosis is thrush, and also the one which is most thoroughly established as an instance where fungi are unequivocally pathogenic. Up to a few years ago, tropical sprue seemed almost established as due to *Monilia psilosis*. Of late, it has been severely questioned. However, this affection is comparatively uncommon in continental United States and need not be dwelled upon. Yeast cells, however, have long been intriguing as met so commonly in the intestinal tract in chronic diarrheal states. They have been studied in pellagra, in the sprue already quoted, pernicious anemia and yellow fever. It cannot be stated, however, that anything definite has been attained in these states. A recent paper by Fleisher¹¹ and Wachowiak, entitled "The Relation of Fungi Imperfecti to Diarrheal Conditions" is an example in point. Just to indicate the diversity of forms under which fungi may produce affections in the digestive tract, let me subjoin the following citations. Chronic monilial infection of the tongue, as reported by Shelmire¹² and by Zeisler,¹³ favus of the tongue by Sequeira,¹⁴ patches of red or black hairy villi on the tongue caused by *torula* or *streptothrices*, by Alvarez¹⁵ and myself.¹⁶ Calculi have been known to develop in connection with these thread accumulations in the salivary ducts (Kapsenberg¹⁷); the pathology is analogous to that of the well-known calculi which occur in the lachrymal ducts, which are also referable to clumps of tangled thread organisms.

With the exception of the widely generalizing fungi previously mentioned, the wall of the gut tract as well as the liver and pancreas appear to be seldom infected by fungi. Just at present microscopic sections are lying on my table in which *actinomyces* were identified by Dr. G. M. Robson of our pathologic department. They appear in the lung and liver of a boy who had been operated upon

for appendicitis; the fungous nature of the appendiceal disease had not previously been recognized or suspected. Foulerton¹⁸ has described *Streptothrix hominis* III and IV in 2 cases of appendicitis, and a lesion of the esophagus has been referred to puncture by a spine of grain which carried with it one of the actinomyces (Langer¹⁹)

The well-known fact that commercial yeast at least acts as a laxative attracts yet more attention to the persistent reports of chronic diarrheas associated with yeast cells in the stool. Scalas,²⁰ in an examination of the sputum and stools of 50 cases, reported an *oidium* in 7 of 11 cases of digestive trouble. Wood²¹ has recently reported experiments which he thinks incriminate *Monilia psilosis* as one of the causes at least of pernicious anemia, but this has recently been disputed by Nye, Zerkas and Cornwell.²² The organisms were recovered only from the gums, not from the granulation tissue at the apices of the teeth.

Details concerning thrush are out of place here. Perhaps the only point that is justified is that this disease, while a clinical entity, is not an etiologic one. Indeed, no less than 18 different organisms have been catalogued by Castellani²³ in his Milroy lectures. *Oidium albicans* is probably the most common offender, but after this three other *oidiums*, a *saccharomyces*, a *hemispora*, a *willia*, an *endomyces*, and no less than ten *monilias* find place. Perhaps this is one explanation of why all cases of thrush do not respond promptly to boric acid medication. A further practical point is that, when present in the mouth, the infection may also be present elsewhere. Thus, it has been found frequently enough in intertriginous positions on babies, indeed, there are instances where the original infection was cutaneous and where the mouth involvement has been the secondary one. Meyenburg²⁴ reports thrush fungus in gastric ulcers. A fatal case involving the skin, lungs and nails is reported by Christison,²⁵ and Riemschneider²⁶ reports fatal bleeding as the result of the erosion of a bloodvessel (esophagus) by thrush.

The Genito-urinary Tract. Except for the widely generalizing fungus infections, this tract does not appear to be commonly parasitized by fungi. There are several accounts, however, a recent one by Rhamy,²⁷ where yeast cells have been passed in large quantities in the urine. It is quite possible that this is not a case of true blastomycosis as indicated in the title, but that it is an example of semipathogenicity, the organisms not actually invading the tissues of the host. The situation is probably analogous to the well known aspergillus infections of the ear and the lachrymal ducts already cited where the organisms accumulate and produce their disturbances mechanically—simply as the result of their mass. Instances of black urine and red urine have been reported in which more or less highly pigmented yeast cells were at fault. The red cases have been erroneously mistaken as instances of hematuria. *Streptothrix urethritidis* has been described in "many" cases of prostatitis by

Schwartz and Cancik.²⁸ Encouraging results were reported from the use of a vaccine prepared from these cultures.

The Nervous System. I do not know of any instances where the peripheral nerves or the substance of the spinal cord has been affected except by extension from a contiguous osseous infection. There are several instances of infection, apart from the well-known actinomycosis and blastomycosis, in which the brain parenchyma has been involved. In infection by *cryptococcus* the organisms extend to the spinal fluid; most important as a diagnostic opening. I have had close contact with one of these cases through the kindness of Drs. Walter Freeman²⁹ and Frank B. Lynch. The symptoms are those of meningitis, and the disease is quite undiagnosable except by finding organisms in the spinal fluid. This is very readily done, and Lynch and Rose³⁰ have reported a case which was diagnosed before necropsy, because they had the acuteness to distinguish yeast cells from degenerate red blood cells. The organism induces myriads of minute, very characteristic mucoid cysts in the brain.

*Actinomyces asteroides*³¹ has been reported as responsible for a number of suppurative lesions of the brain, but numerous other thread organisms have also been scatteringly met.

Eye. Gifford's³² papers contain extensive data on sporotrichosis of the eye and on mycosis in general; likewise, Landrieu's³³ thesis.

Aspergillosis of the cornea has been reported by de Schweinitz.³⁴ Lachrymal calculi have long been known as due to massive entanglements of *Actinomyces foersteri*³⁵ which occlude the duct and may lead to secondary infection. This species is eminently benign, it does not have the significance that actinomyces have as ordinarily thought of.

Ear. The only fungus affection of which I am aware in this position is a more or less mechanical obstruction by aspergilli. The organism usually does not invade the surrounding tissues, but simply acts as an impediment. There was a small epidemic of otomycosis in Florida following the hurricane³⁶ of September, 1926; it appears that heat and moisture favor growth of the fungus, and proliferation is also favored by the instillation of oil. These should, therefore, be avoided. Being a surface affection, iodid of potassium internally has no effect, although it might be tried in the rare instances where suppuration and penetration of the ear drum has taken place. (Koenig.³⁷) Besides *Aspergillus nigra* and *fumigatus*, *Actinomyces cylindraceus* (Korte³⁸) and *Cephalothecium roseum* have been regarded as causative.

Bone. This claims the interest of the surgeon particularly. Sporotrichosis, actinomycosis and blastomycosis notoriously determine to bone, giving symptoms that are easily confused with those of tuberculosis. A wide variety of fungi has been described producing what are rather uniformly denominated as "gumma-like" swellings of the bone. Indeed, "sporotrichotic gummas" has become the

conventional terminology in that affection. One of the first and, therefore, historic instances of bone infection in human beings by yeast cells affected the tibia, by *Saccharomyces hominis* (Busse³⁹). Just at present I am studying smears and culture referred to me by Dr. David L. Farley of the Pennsylvania Hospital. The pus from an unopened lesion on the skin shows tremendous numbers of sausage-shaped, sometimes budding, yeast cells. At least one case of generalization with fatal outcome is known, due to infection with *Cryptococcus hominis*.²⁹ Another instance of osseous gummas is referred to *Cryptococcus breweri*.⁴⁰

The Integument. Here we come upon a field literally ridden with fungus infection, quite understandable. It is impossible to shop even rapidly through the entire list of species; I shall at once pass by the ordinary ringworm of the scalp and the banal tinea circinata, sycosis, and so forth, but must pause long enough to emphasize the most recent addition to, or better recognition of, fungus expression upon the skin. I refer to dermatophytosis.

In short, this is nothing more nor less than a fungus infection which, first, is superficial (that is, excludes deeper affections like blastomycosis) and which, secondly, generally has an affinity for intertriginous positions. This, however, is not always the case; and then the diagnosis is rendered correspondingly difficult.

The general practitioner ought to diagnose dermatophytosis for himself from the eczema with which it is likely to be confounded—he will be served best in this by its localization; that is, usually intertriginous position. Once he suspects dermatophytosis, he can check up in the following way: first, determine whether the margins are sharply outlined; if so, this very strongly fortifies the diagnosis. Second, is there a delicate collarette of epiderm extending around the margin? Again, this is helpful toward the diagnosis. Finally, the direct examination of scrapings under the microscope is often a final and unequivocal answer to the question. This is a very simple laboratory procedure (Weidman),⁴⁵ really, it is an office examination rather than laboratory, and one which should be applied by all those who wish to keep abreast with modern practice.

The importance of dermatophytosis will come home to you when I tell you that 67 per cent⁴¹ of a university student group were found to be affected by the disease in the form of ringworm of the toes. The well-known “jock-strap itch” and ringworm of the axilla also come in the category of dermatophytosis.

Therapeutics. If there is any one most useful agent in the attack upon fungus infection it is iodine. This has been recognized for many years; not alone as a local remedy but also internally. It can be administered both in the form of potassium iodid and Lugol's solution. It has been most valuable in blastomycosis and in miscellaneous surface infections, but occasionally brilliant results are secured in actinomycosis and even in other more refractory fungus

infections. With the advent of the Roentgen rays, success became even more frequent; most commonly the two agents, iodine and Roentgen rays, have been used in conjunction.

A very practical point in iodine therapy is that the dosage should be large. It is possible, beginning with the usual 5 to 10 grains three times a day, to increase up to as much as 120 grains three times a day, or even more.

It is surprising what large doses of Lugol's solution can be administered intravenously. Shelmire⁴² has called our attention to this in this country in treating sporotrichosis. He administers as much as 10 cc. of Lugol's solution, diluted by 100 cc. of normal salt solution, and has had striking results. In France, particularly, but elsewhere, this avenue has been employed in various other fungus infections with excellent results. I know of one failure in the treatment of a particularly obstinate thrush at our University Hospital.

Thallium acetate⁴³ is another recent addition to our armamentarium; it is thus far confined to treating ringworm of the scalp, having value solely because it produces epilation. Administered orally in the dosage of 8 mg. per kilo of body weight, it causes the falling out of the scalp hair in sixteen to eighteen days. Comparatively uniform success has been reported both in this country and abroad from the use of this most valuable addition to the treatment of fungus disease, but there are dangers and the literature should be consulted before practising it.

In the treatment of the more superficial dermatoses, such as the well-known tinea circinata of children, almost any antiseptic will suffice; the copper penny of the housewife, dipped in vinegar, serves the purpose very well. Tincture of iodine, salicylic acid ointment, 5 per cent, and various other antiparasitides are effective.

As to dermatophytosis, treatment largely depends upon the part of the body which is affected. On other positions than between the toes, the disturbance usually yields readily upon the application of lotions or ointment of salicylic acid, ammoniated mercury, and other well-known fungicides. There are changes that must be rung when treating this class of fungus affection, depending upon the stage of the disease; thus, when acute, milder applications and when chronic more powerful and stimulating ones. In ringworm of the toes I have come to place most reliance on salicylic acid ointment. This is most conveniently applied in the form of Whitfield's ointment, in which the salicylic acid is represented in a strength of 20 grains to the ounce. It is better to use Lassar's paste as a base because it is more adherent and is less likely to be absorbed by the clothing. Other authorities prefer tincture of iodine, mercurochrome, and various other fungicides. The usual experience in these cases is that there is marked improvement up to a certain point; eventually, all that is left between the toes is a small, circumscribed, white, sodden patch of thickening, which effectually resists further

treatment. As a rule, treatment is discontinued by the patient at this time because the affection is no longer an inconvenience; however, the fungi are still present and constitute a reservoir, a focal infection, which threatens at any time to extend to the dorsum of the foot or elsewhere upon the body. One of the most important problems in fungus affection of the skin today is a certain cure for resistant cases of ringworm of the toes.

Tartar Emetic. Guy and Jacob⁴⁴ are responsible for discovering that this drug promises much in the treatment⁴⁵ of the hitherto invariably fatal coccidioidal granuloma. Tomlinson has just confirmed this—a laboratory infected case which otherwise would have progressed to a fatal outcome. The drug is administered intravenously, beginning with 3 cc. of a 1 per cent solution and increasing up to 10 cc. Occasionally there is a constitutional reaction, but this must be endured in view of the otherwise absolutely black prognosis in this disease.

Summary and Conclusions. The various organic systems have been considered in their relation to fungus disease with many indications that fungi are important in modern medicine.

Among the outstanding modern mycological advances, from the diagnostic viewpoint, we have the waxing rôle of pseudotuberculosis, the ubiquity of dermatophytosis, and the possibility of yeast cells being present in bone abscesses and meningitis. Therapeutically, we have as much or more "modernism" in the employment of the Roentgen rays, and medication with thallium acetate, tartar emetic and iodine intravenously.

As physicians we must recognize that:

1. Almost every organ and kind of animal tissue is liable to fungus infection; none of the specialties, except possibly gynecology and obstetrics, is exempt from concern with this class of disease.

2. The profession, if not already cognizant of a certain though minor rôle of fungi in disease, is not addressing itself seriously or continuously enough to the situation.

3. The physician must depend almost entirely upon the laboratory for the detection of fungus cases, particularly in nondermatologic ones and in such important affections as pulmonary pseudotuberculosis.

4. Therefore, the average general laboratory man is largely at fault for our mycologic backwardness because he is not adequately trained in mycology. There is need for at least a few mycologic centers in conjunction with general pathologic laboratories, regionally distributed through the United States.

5. Modern intravenous and other methods of therapy are reinforcing the honored and efficient iodine and Roentgen ray modalities. These, consequent of course only upon accurate diagnosis, should not be denied to the small but still appreciable proportion of fungus patients.

There was an interesting history of rheumatism in this family. Her father had had repeated attacks of rheumatic fever, two sisters and two brothers had also suffered from this disease and the impression received on her admission to the hospital when first examined was that of definite rheumatic fever.

The tonsils showed no gross pathology and the only points of interest, aside from the acute arthritides were the many decayed teeth and the herpes labialis.

She was put upon large doses of salicylate by the bowel, 10 gm. daily for five continuous days, after which salicylates were given by mouth in smaller dose. However, on several occasions subsequent to this course of treatment, she received large doses of salicylate by bowel. We seemed to get the usual response of rheumatic fever to salicylates and at the end of three weeks, the temperature was normal and when taken over by us on the first of September, was looked upon as a convalescent rheumatic-fever patient with no apparent cardiac involvement. There is one interesting diary note made by an assistant, who examined the heart on admission, which states that the aortic and pulmonary first sounds were very indistinct.

After a very brief period, this patient developed an intermittent fever with marked diurnal variation, which at times assumed a remittent type and this continued up until the time of her death, November 12, 1927, a period of about ten weeks. Repeated blood cultures showed no bacteriemia. The blood was also tested for malaria, there being some suggestion of estivo autumnal fever, particularly in the presence of a palpable spleen and here the findings also were negative. Two catheterized specimens out of nine examinations of urine enabled us to eliminate the possibility of a pyelitis. The leukocytes ranged in an ascending curve from 12,800 to 20,400 with a corresponding increase of polymorphonuclear leukocytes extending over a period of ten weeks. This patient from the start had almost daily vomiting, which we were unable to help or find the cause of. The oral hygiene was fair except for the old tooth roots. The right ankle and the right wrist presented a focal arthritis, particularly the wrist which suggested a lesion of Neisserian origin, but a pelvic examination made by the gynecologist showed these organs to be normal. After a study of six weeks we were able to find infected teeth as the only possible foci of infection. A few days later, when our working diagnosis was recorded as septicemia, there developed over the precordium definite adventitious sounds, both in the mitral and aortic areas and over the base of the heart a rub, strongly suggesting pericarditis. This development, with the presence of a capillary pulse, made us then feel that the patient was suffering from a bacterial endocarditis of a subacute type. Subsequent study went to confirm us in this opinion. The blood pressure on two occasions was 108 systolic, 72 diastolic, and 118 systolic, 66 diastolic. Fourteen weeks after admission the patient died, having developed a unilateral parotitis two days before death. The principal clinical diagnosis was bacterial endocarditis.

At necropsy there was little evidence of the parotiditis or of the arthritis of the right wrist. The principal findings were in the heart. On removing the heart a firm, yellow, finger-like process was seen to protrude from the right heart, out into the pulmonary artery. When the heart was opened, this was found to be the tip of a large solitary vegetation, involving at its base all but a rim of the posterior cusp of the pulmonary valve. The other pulmonary leaflets showed no evidence of pathologic change. The vegetation was ovoid and measured about 2 by 1.5 by 1 cm. Several smaller vegetations were situated on the mural endocardium of the conus about 0.5 cm. away from the larger one, and one of these appeared to be ulcerated. Microscopically, this was confirmed. The smaller vegetations were found to be fairly well organized except at the immediate surface. Gram-

Weigert stains of the large vegetation revealed Gram negative intra- and extracellular organisms which morphologically were identical with the gonococcus. Culture of the vegetation was not made. The base only of this vegetation showed beginning organization. All the other valves were free, save for a few minute sclerotic thickenings on the mitral leaflets. The myocardium showed a mild degree of fibrosis and some cloudy swelling. It was thought in the gross that a wide irregular scarlike area in the left kidney was the result of old infarction, but on microscopic section the only changes were a very slight increase of the fibrous stroma and a few organized and hyalinized glomeruli, together with some sclerosis of the vessels. The only explanation that remained was that it was the result of vascular sclerosis and that gradual occlusion of a moderate-sized vessel had occurred. The liver was extremely large, weighing 2700 gm., and aside from a fatty infiltration showed a true acute hepatitis, with areas of infiltration by polymorphonuclear leukocytes and lymphocytes. The spleen was large and flabby and of the toxic degenerative type. The internal genitalia showed a bilateral cervical laceration and a chronic salpingitis. The latter is most interesting in view of the possible Neisserian origin of the disease. But the evidence was not quite enough to convince one that this was the primary focus. The case was summed up thus—"The valvular lesion was apparently one of recent development. The causative factor is probably the gonococcus. Clinically the case resembled in some respects one of subacute bacterial endocarditis."

CASE II.*—A man, aged sixty-eight years, was admitted to the hospital on May 17, 1923, in a semicomatose condition. He had been found lying in a shed and was brought in by the police. No other history was obtainable. Physical examination showed an undernourished individual, a few moist râles at the bases of both lungs, some lateral enlargement of precordial dullness with a systolic murmur at the apex and accentuation of the second pulmonic sound and marked edema of both lower extremities. Blood pressure was 102 systolic, pulse 90 to 138, temperature not given. He was catheterized and relieved of 26½ ounces of urine. He died a few hours after admission.

The principal autopsy findings were acute lobar pneumonia (left lower), acute vegetative pulmonary endocarditis (pneumococcic) and acute verrucous mural endocarditis (streptococcic), and acute suppurative cerebrospinal meningitis (pneumococcic). The vegetation on the pulmonary valve was the point of especial interest. *In situ* this vegetation plugged and occluded, in death, the orifice, a large sessile soft mass, unorganized and partially necrotic, measuring 3.4 by 2.2 by 2 cm. and attached to the anterior cusp and, save for a narrow margin at the base, involving the entire cusp. Although the base of the vegetation was on the under surface of the cusp, the bulk of it was directed upward into the pulmonary artery. The mural endocardium adjacent showed several small vegetations. Smears and cultures of the large vegetation and of meninges showed pneumococcus. Culture of the mural vegetations showed a hemolytic streptococcus.

Comment. The things worthy of note in these cases seem to us twofold; first, the comparative rarity of acquired pulmonary valve lesions, and second, the probable origin of the vegetations, from a bacteriologic view point. The point of first interest is the rarity of such lesions. Of 24,000 consecutive admissions to the Johns

* By courtesy of de Wayne G. Richey, M.D., sometime pathologist to Mercy Hospital.

Hopkins Hospital, there were only three who showed signs of pulmonary regurgitation.¹ Figures on stenosis are not available, but though more frequent in its occurrence, stenosis is so uniformly of the congenital type that mention of acquired stenosis could not be found. At the Mercy Hospital, between the years of 1910 and 1926, there have been 1192 autopsies. Of these, 18 were in cases of acute endocarditis (including cases of acute and recurrent endocarditis). Only 2 previous cases (0.16 per cent) showed vegetations on the pulmonary valve and one of these was associated with vegetative endocarditis of all the other valves. The other was Case II of the present paper. In this older case, the pneumococcus was isolated, and the lesion was associated with a lobar pneumonia and a pneumococcic meningitis. Incidentally there were in the Mercy group² 2 cases of gonococcic endocarditis, neither of which involved the pulmonary valve. Autopsy records at the University of Pittsburgh from 1908 to 1924, exclusive of the Mercy group, showed the following results. Of 803 autopsies, the pulmonary valve showed two acute vegetative or ulcerative lesions, one of which occurred on the pulmonary valve alone. It was noted that each of the acute lesions was associated with a congenital lesion or with an acute infection. The percentage of acute lesions in the University group was 0.25 per cent.

The etiology in the first case is not definitely proven; that in the second case quite definite. Bacteria have usually been demonstrated in cases of acute endocarditis, either from the heart's blood or vegetations and these belong almost entirely to the group of pyogenic cocci. Bacteria such as the influenza bacillus, *Bacillus typhosus*, and *Bacillus dysenteriae* have been isolated in rare instances. The most common organisms, however, in order of frequency are, the streptococcus (hemolytic and nonhemolytic), the staphylococcus, the pneumococcus and the gonococcus.³ The gonococcus falls last in the group but is classed by all writers as one of the common exciting causes of acute endocarditis. Of 176 cases of acute endocarditis, 20 (11.3 per cent) were gonococcal. When the question of pulmonary-valve endocarditis is considered, the situation is reversed. Of gonococcic endocarditis cases from the Johns Hopkins Hospital, 25 per cent showed pulmonary-valve involvement; of all gonococcic cases in the literature (80 in number until 1922) 12.5 per cent were on the pulmonary valve. In all reported cases (1922) of *Streptococcus viridans* infection of the endocardium, only 7.6 per cent involved the pulmonary; of hemolytic streptococcus, 7.6 per cent; of *Staphylococcus aureus*, 4 per cent; of *Staphylococcus albus*, 0 per cent; and of pneumococcus, 4 per cent. It will thus be seen that the gonococcus attacks the pulmonary valve from two to three times as frequently as its nearest competitor for that position, the streptococcus. Of cases collected by Pitt from Guy's Hospital, London, nearly one-half of pulmonary

valve lesions in which a definite infectious cause was ascertained were due to the gonococcus.⁴ Barker, of Johns Hopkins, states that all forms of endocarditis in fetal life tend to affect the right side of the heart; in adult life it is only the gonococcic form which shows this tendency.⁵

An interesting comparison of the average duration of the various acute endocarditides is made by Thayer⁶ as follows:

	Weeks.
<i>Bacillus influenzae</i>	28.0
<i>Streptococcus viridans</i>	23.1
<i>Gonococcus</i>	10.5
<i>Staphylococcus albus</i>	6.8
<i>Staphylococcus aureus</i>	4.5
<i>Pneumococcus</i>	4.3
<i>Streptococcus hemolyticus</i> , less than	3.0

It will be noted that Thayer brings what is usually termed the subacute type into the group of acute endocarditis. In this, we have concurred throughout this paper, believing them all to be variations of the same type of pathologic process. The point of especial interest in connection with the present case (case one) is the fact that the duration of our case from the onset of septicemic manifestations was just about ten weeks, or the average time of the gonococcic form of the disease. Also, on further study of the table, it is noticed that the difference between this and those most nearly approaching it in duration is quite wide, the green streptococcus cases lasting about twice as long, the staphylococcus cases only about half as long.

Differences in the morphology of the vegetations occur and have some significance in identifying the type of infecting agent. Vegetations vary in size from pin-point to those occluding a whole valve orifice. Two types deserve mention; first, the vegetations of subacute (*Streptococcus viridans*) endocarditis, though occasionally large, are usually rather small and multiple. They occur most frequently on the mitral valve (two-third of cases), and the aortic valve, or both, and tend to extend upward onto the wall of the left auricle. They are almost invariably engrafted on old sclerotic valve lesions. Second, staphylococcus, pneumococcus, and gonococcus vegetations are larger, less organized, and often pedunculated. They are frequently associated with ulceration, rupture, or the formation of mycotic aneurysm.⁷ Of 20 cases of gonococcic origin at the Johns Hopkins Hospital, 19 showed large vegetations and only one, small ones.⁶

In view of the foregoing discussion, it seemed possible to us to eliminate certain etiologic factors from our first case: (a) Influenzal endocarditis is quite rare, for, few cases could be found in the English literature. The present case had no preceding influenzal history and the duration of the disease was too short. Arthritis is

not described as associated with the influenzal form. (b) Pneumococcic endocarditis is too brief an illness for our case (though at the time of writing there is in the hospital a case showing pneumococcus in repeated blood culture for the past six weeks), and there is no antecedent history of pneumococcic infection. But most important is the repeatedly negative blood cultures. (c) Staphylococcic endocarditis can, we believe, be eliminated by the absence of pyemic manifestations, the sterile cultures, and the duration, which is much too long. (d) Rare forms, such as typhoid and dysentery, seem most unlikely and there is no suggestive evidence in their favor. This leaves but two remaining types to be differentiated, namely, the nonhemolytic streptococcic form and the gonococcic. We sum up the evidence for and against each in the ensuing paragraphs.

In favor of the nonhemolytic streptococcus in our case are the following: The rheumatic type of history and history of rheumatism in the family; and the fact that this is comparatively the more common form. Whether the early response to salicylates is evidence of streptococcic infection is open to debate. Arguments against the *Streptococcus viridans*, as an etiologic factor, are: The relatively short duration of the illness; the repeated sterile cultures; the large size of the vegetation, and the absence of embolic phenomena. In favor of gonococcic endocarditis, the outstanding points are: The duration was (almost too remarkably) the exact average duration found for this disease; the pulmonary valve was attacked, the valve so much more frequently involved by the gonococcus than by any other organism: the vegetation was large; the lesion was preceded by an arthritis that at least in one joint was of a destructive nature; the repeatedly negative blood cultures in the presence of such an intense process points to the gonococcus rather than any other organism: the presence of chronic salpingitis, though not certainly due to the gonococcus, is suggestive; the numerous miscarriages and the early death of several of her children point in the direction of venereal disease; and finally, the presence of Gram-negative intracellular diplococci in the vegetation points strongly to the gonococcus. Unfortunately, no direct smear was made; the examination for organisms being made on sections of the vegetation stained by the Gram-Weigert method. Arguments against the gonococcus are: the relative infrequency of its occurrence (11.3 per cent of 176 cases of acute endocarditis⁶), and the absence of a definite acute focus of infection.

Summary. 1. Two cases of uncommon cardiac pathology are presented and discussed.

2. The etiology in one case is culturally positive; the other analytically and presumptively definite.

3. The clinical diagnoses were correct for gross pathology of the endocardium, but not for the valve involved.

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BILATERAL ANEURYSMS OF THE COMMON ILIAC ARTERIES.

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A CASE of bilateral aneurysm of the common iliac arteries is herewith reported, which is noteworthy on account of its extreme rarity as well as for some clinical facts which permitted the recognition of one of the aneurysms intravital.

Case Report. M. L., aged fifty-eight years, male, white, married, Austrian by birth, real estate operator, was first seen at his home on May 26, 1928. His chief complaint was severe pain in the lower abdomen, vomiting, extreme weakness and inability to empty his bladder. His mother died from a cancer (organ involved not known) and one brother died at the age of forty-five years of cancer of the stomach. At the age of twenty-two, the patient had an appendectomy, and nine years ago he was operated upon for hemorrhoids. At the age of twenty-eight, he had an uncomplicated gonorrhea. About three years ago, while driving his car, he was suddenly seized with a severe pain in the left chest and arm. He consulted a physician who advised absolute rest. He then entered a sanatorium where he remained for about three weeks. While there he had several attacks of precordial pain, which promptly yielded to inhalations of amyl nitrite. On the day of his discharge from the sanatorium he had an unusually severe attack accompanied by staggering gait to the right, double vision and weakness of the left arm. He entered the United Israel-Zion Hospital for further study on December 6, 1925.

On examination, his heart was reported as slightly enlarged to the left. No murmurs, irregularities or accentuations of A2 or P2 were found. The

pulse rate varied from 65 to 90, and the blood pressure was 130 systolic, 90 diastolic. There were no abnormal findings in the chest or abdomen. There were marked sclerotic vascular changes in the retina. The neurologic findings were: Lateral and vertical nystagmus, cerebellar type of speech disturbance, coarse, jerky movements of the fingers of both hands, with ataxia in the finger-to-nose and heel-to-knee tests more marked on the right. There was marked ataxia on walking, with a tendency to fall backward and to the right. No evidences of pyramidal-tract involvement was present. These findings point to an olivo-pontine-cerebellar disturbance. The pain in the left arm may be thalamic, but an anginal origin must be excluded.

Laboratory Examinations. Wassermann test, negative; urine, normal. The hemoglobin was 75 per cent and the red cells were 4,000,000; the leukocyte count, 6800. Chemical examination of the blood revealed normal findings. A Roentgen ray study of the chest showed the heart to be of the hypersthenic type with moderate left ventricular hypertrophy. No deformity characteristic of any valvular defect was observed. The aortic arch was unusually broad and dilated, suggesting a fusiform enlargement due to a loss of elasticity.

During his stay at the hospital, the patient had several severe anginal attacks which yielded to nitrites. His general condition improved, his speech disturbance, ataxia and nystagmus became less marked, and he was discharged from the hospital on December 18, 1925, with the diagnosis of probable pontine hemorrhage, arteriosclerosis and aortic dilatation.

His interval history from the time of his discharge to his present illness was not obtained. On May 25, 1928, at about 4 P.M. he was seized with terrific pains in his lower abdomen as if something had burst. He fainted and his family physician was summoned. The next morning he vomited a coffee-ground material which on examination was found to contain blood. He had not voided in about twenty hours and on catheterization a few ounces of bloody urine were recovered. The patient was in collapse, extremely pale and drenched in a profuse perspiration. His radial pulses were imperceptible and the heart sounds were rapid and feeble. Both a systolic and diastolic murmur were present at the third left intercostal space at the sternal border. His pupils were contracted and rigid, possibly the effect of morphin. The lungs were negative. In the left lower abdominal quadrant there was a tender pulsating mass measuring about 15 cm. in the longitudinal and 10 cm. in the transverse diameter. It extended from about the midabdominal line to the left iliac crest and into the left flank. No bruits were heard nor were any thrills palpated. Rectal examination was negative except for prostatic hypertrophy. A bilateral varicocèle was present. A tentative diagnosis of a ruptured or dissecting aneurysm of the left common iliac artery was made. The possibility of an encapsulated hemorrhage was considered, and the patient was advised to enter the hospital. He was admitted on May 26 at about 3 P.M.

The next day the abdominal mass had extended to the left costal margin. There was dullness on percussion over the mass. Free fluid in the peritoneal cavity could not be demonstrated. Pulsations were present and equal in both femoral arteries. On catheterization, about 1 ounce of dark urine was obtained. A surgical consultation was requested and the findings were confirmed and expectant treatment was advised. At about noon that day, while an attempt to estimate the blood pressure in the left popliteal artery was being made, for comparison with that in the right, the patient suddenly screamed because of excruciating pain in his left lower abdomen, went into shock and expired in about an hour. His temperature range was from 97 to 100.6°, hemoglobin 60 per cent and the red cells were 2,320,000. The leukocytes numbered 8000.



FIG. 1.—Roentgenogram, showing diffuse dilatation of the aorta.



FIG. 2.—Aorta and common iliac arteries opened from behind. Large intramuscular and retroperitoneal hematoma over left aneurysmal sac.

Autopsy Record. The body is that of a tall, well-built male. The abdomen is distended and tense. On incision, a small amount of bloody fluid was found in the abdominal cavity. The apices of the lungs are adherent to the chest wall. On section a considerable quantity of frothy fluid oozed from the cut surfaces of the lungs. The heart is enlarged and the musculature of the left ventricle measures about $2\frac{1}{2}$ cm. in thickness. The valves are thin and smooth. The aorta is diffusely dilated from its origin to its abdominal portion. The ascending arch shows just a few normal areas between which are scattered many atheromatous ulcers. There is scarcely any intact intima present. Hard, elevated, almost cartilaginous areas of white fibrous tissue alternate with yellow patches and definite atheromatous ulcers. Most of the fibrous areas are located about the mouths of the intercostals and other arterial branches. Both common iliac arteries are transformed into oval sacs about the size of a fist, the left being the larger. The sacs are partly filled with laminated thrombi. Toward the aortic end of the sac of the left common iliac artery, there is a perforation about the size of a silver half dollar with enormous hemorrhagic infiltrations of the adjacent structures. There is a large tumor mass on the left extending from the diaphragm into the left pelvis. This mass communicates with a similar mass extending into the right pelvis. These masses are covered with peritoneum and are hemorrhagic infiltrations of the iliopsoas muscles and perirenal fatty tissues. The smaller mass is the right common iliac artery surrounded by hemorrhagic infiltrations. The liver and spleen are slightly enlarged, the adrenals are pale with the cortex slightly larger than normal. The kidneys are medium-sized and the capsules strip with difficulty. The kidney substance is pale and the surface granular.

The pathologic diagnosis was atherosclerosis of the aorta with diffuse dilatation and bilateral aneurysms of the common iliac arteries. The left was dissecting and perforated, with infiltrations of the perirenal tissues. Edema of the lungs, cardiac hypertrophy and adhesive pleurisy were present.

This case is of unusual interest because of the presence of bilateral arteriosclerotic common iliac aneurysms. Vascular disease of the aorta and cerebral vessels was clinically and radiographically recognized about two and a half years before the patient's present admission. At that time, abdominal examination did not reveal the presence of any pulsating abdominal masses. The onset of his first symptoms, three days before his death, was probably due to a rupture of the intima of the aneurysm with a dissection of the coats of the vessel. The perforation and retroperitoneal infiltrations which seemed of recent origin most likely occurred at the time of the blood-pressure determination in the left popliteal artery. This procedure probably increased the tension in the aneurysmal sac. The pathogenesis of this double aneurysm is obviously based upon the general sclerosis of the arterial system. There were advanced changes throughout the aorta resulting in a diffuse distention. There were clinical evidences of cerebral vascular disease. No evidence in favor of syphilitic infection could be obtained either from the history, from the postmortem appearance of the organs or from the serology. As a matter of fact, syphilitic aneurysms have a tendency to localize

in the ascending aorta or peripheral vessels. Syphilis seems to spare the larger intermediate vessels. Aneurysms of the descending and abdominal aorta or its larger branches are usually due to atherosclerotic changes.

In reviewing the literature, we have been able to find only two reported cases of bilateral common iliac aneurysms. These cases were reported by Sternberg¹ and by Barber.² While aneurysms of the external iliac artery are comparatively frequent, those of the internal iliac are rare, and those of the common iliac artery are still rarer. Matas³ quotes only 2 cases of common iliac aneurysm among 172 cases of aneurysms of the large arteries of the lower extremities. He refers, however, to the statistics of Crisp⁴ who is said to have found 11 cases among 551 aneurysms of the iliofemoral vessels. Wedekind,⁵ Hinsdale,⁶ Montillier,⁷ Maynard⁸ and Rivet⁹ have each reported unilateral common iliac aneurysms. The case reported by Sternberg¹ resembles our case. Barber's² case was found during the course of an exploratory laparotomy. The data concerning the etiology of the reported cases in the literature are rather scanty. Sternberg's case bears the earmarks of a general atherosclerosis in a senile person. There is nothing in Barber's report which could possibly elucidate the pathogenesis of his case. The same applies to most of the cases of unilateral aneurysm of the common iliac artery which we could gather from the older literature. Localization of the aneurysmal distention of the common iliaes is rather unusual, and we are unable to find or offer any explanation for its occurrence in these arteries.

Summary. The case presented is that of a bilateral aneurysm of the common iliac arteries of arteriosclerotic origin in which syphilis was definitely excluded. Diagnosis was arrived at by palpation of a large pulsating mass in the left lower abdominal quadrant, which increased in size during the period of observation. There are only two similar cases reported in the literature.

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TWO CASES OF PERIARTERITIS NODOSA. ONE WITH UNUSUAL MANIFESTATIONS (MENINGEAL FORM).

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PERIARTERITIS nodosa is a rare disease, mainly affecting the small and medium-sized arteries throughout the body. Its rarity is indicated by the facts that it was found in only 2 of the 2035 autopsies performed at the Peter Bent Brigham Hospital and in a recent survey of the literature¹ only 130 cases were uncovered. The disease was first described as a distinct clinical entity by Kussmaul and Maier² in 1866 and since then it has been found to exist in a variety of clinical forms. Inasmuch as the underlying, if not the sole lesion, affects the bloodvessels and the injury is very widespread, it is obvious that the symptoms produced will depend upon the particular organs involved. Although vessels of the heart and kidneys are affected very frequently, changes in other organs may predominate and produce the presenting complaints. The patient often complains of pains in the extremities, occasionally in the abdomen, runs an atypical fever with leukocytosis and may develop a number of peculiar symptoms to be classified below.

The specific cause of the disease still remains unknown. However, the febrile course, which lasts from two to several months, and the similarity of the pathologic findings to those observed in Rocky Mountain spotted fever³ and typhus fever⁴ make it very probable that it is infectious in nature. In fact, there are lesions in other infections such as those found occasionally in the small bloodvessels in influenza (cerebral vessels), and epidemic meningitis (skin capillaries),⁵ that are not unlike those described in this disease. It is still an open question as to whether periarteritis nodosa is a specific entity or an unusual vascular manifestation of a variety of infections. The latter view was maintained by Gruber,⁶ who believed the arterial lesion to be an allergic phenomenon resulting from different infectious agents. The great rarity of such lesions in the many infections that exist and the uniformity of the pathologic findings, when they are seen, make us lean toward the specific nature of the disease.

The particular symptoms and the predominating involvement of certain organs have led to the classification of the following

types of the disease: renal, cardiac, abdominal, neuromuscular, cerebral and dermatologic. The renal type may run a course similar to a vascular nephritis, with symptoms of hypertension, renal insufficiency and failing vision. Other cases may suggest infarction with hematuria. The cardiac type results from a predominant involvement of the coronary arteries. Here, the clinical picture is not unlike the ordinary one seen in coronary sclerosis resulting in symptoms of angina pectoris or myocardial insufficiency. In the abdominal type, symptoms and physical signs of an acute abdominal condition are frequently encountered. One can readily understand the difficult position in which the surgeon finds himself when the patient presents the picture of severe abdominal pain, has a fever and a leukocytosis. It is in this type that the antemortem diagnosis is most commonly made, the nodosities being found in the intraperitoneal bloodvessels. The neuromuscular symptoms are usually present to some degree in all types. These consist of pain and tenderness in the muscles and along the nerves of the limbs and frequently are the earliest complaints. The cerebral form is more rare but has been noted by Fletcher⁷ and Dickson⁸ and in our more recent case. In the case reported by Dickson, the symptoms of an acute meningitis were very pronounced and yet the spinal fluid did not reveal any cellular or bacterial evidence of such an inflammatory condition. Case II here reported however, showed a marked elevation of the polymorphonuclear leukocytes in the cerebrospinal fluid during the active stage of meningitis although no organisms could be discovered in this fluid. Cases of the cerebral group, because of the nature of the disease, sometimes simulate infarction or hemorrhage of the brain.

It is the purpose of this paper to record one more typical case of periarteritis nodosa and to call attention to some peculiar features in the second case.

Case Reports. CASE I (Med. No. 24855).—A white American man aged twenty-two years, with an essentially negative family and past history, entered the Peter Bent Brigham Hospital complaining of weakness and loss of vision. Eighteen months before admission he awoke with a right facial paralysis. The paralysis cleared up rapidly but his physician found his blood pressure to be elevated. Three months before entry he began to complain of severe headaches and felt dizzy, with these symptoms he noticed progressive loss of vision.

Physical Examination. This revealed a thin, pale individual with a systolic blood pressure of 245 mm. and a diastolic blood pressure of 146 mm. The eyes were prominent, the disk margins blurred, the cupping gone and the retinal arteries were tortuous and showed flame-shaped hemorrhages.

Clinical Pathology. This showed no very important change except for slight anemia, a leukocytosis of 19,900, a slight trace of albumin in the urine and fairly numerous hyalin and granular casts.

Four days after admission the patient developed severe epigastric pain, a fever of 103.8°, a marked right sided abdominal tenderness and collapsed. He then improved for about two weeks when he suddenly developed

convulsions of a generalized nature. These recurred for four days and then he began to clear up mentally. His leukocytosis persisted, his blood pressure remained high and his eye sight continued to fail. About two months after admission slight edema was noted, purpuric spots were found over the arms and chest and at the same time his blood-urea nitrogen which had remained around 15 mg. per cent slowly rose to 70 mg. per cent. Death with generalized convulsions occurred nine weeks after admission or about five and one-half months after the onset of the presenting complaints.

Pathologic Report. An autopsy performed fourteen hours postmortem, limited to an abdominal incision revealed multiple nodules along the course of the coronary arteries, and a branch of the right renal and hepatic arteries. These nodules varied in size from 1 to 4 mm. in diameter and were very firm and fibrous in consistency. On the under surface of the liver in the region of the gall bladder was a mass of blood clot measuring 6 cm. in its greatest dimensions. The clot appeared grossly to have originated from the substance of the liver adjacent to the gall bladder. Microscopically, the above-mentioned dilatations of the arterial walls in addition to mural thickenings and aneurysmal dilatations, showed a heavy cellular infiltration of the wall and surrounding tissue. In the liver adjacent to the organizing blood clot several small arteries showed endothelial-cell proliferation and a cellular infiltration of the vessel walls themselves.

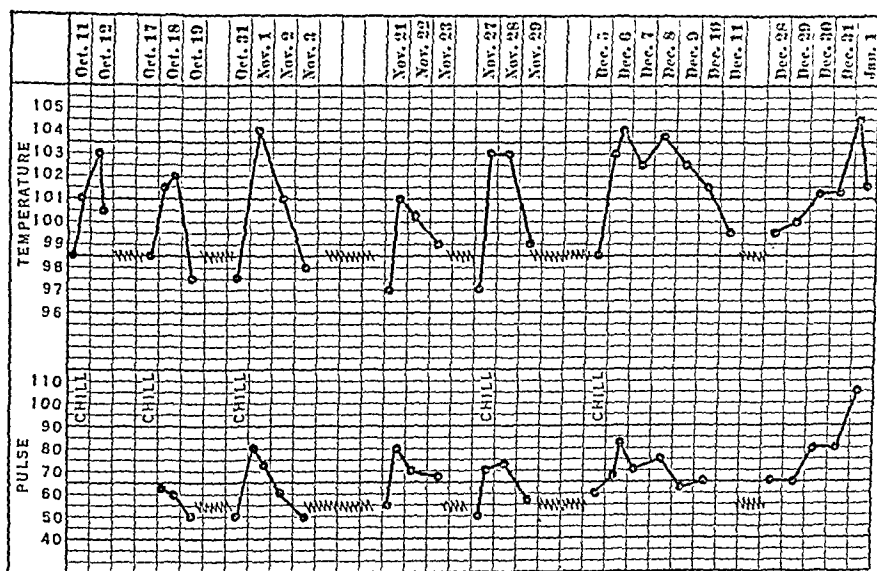


FIG. 1, Case II. A condensed temperature and pulse chart of the entire illness, showing the high fever which occurred at intervals, accompanied by five major chills. The jagged lines represent practically afebrile periods. The low pulse rate even with high fever is a noteworthy feature.

CASE II (Surg. No. 30087).—A retired business man, aged seventy-one years, entered the hospital November 12, 1927, complaining of pains in the arms and legs.

Past History. He had had attacks of biliary colic for the past fifteen years. June 18, 1925, cholecystectomy was performed and numerous gall stones were removed. He was in excellent health after this except for occasional pains in the right big toe (question of gout) and slight dysuria and frequent urination for the past ten years.

Family History. Negative.

Present Illness. Sometime in the late spring of 1927, while in Italy, he had a minor illness for a few days with some generalized aches and pains but no attention was paid to them. He felt quite well after this until August when he began to have troublesome pains in the arms and legs. They grew worse, were intermittent and shooting in character with a feeling of a dull ache between times. There was exquisite hyperesthesia of the skin with this. About September 1 he had to go to bed where he has remained ever since. Upon diathermic treatment the legs improved but the pain in the arms persisted. Looking for a focus of infection both maxillary sinuses were found to be cloudy, especially the right. This was, therefore, punctured but no pus found. October 11, the patient had a sudden chill, temperature rose to 102.6° . The temperature returned to normal in thirty-six hours. Seven days later, October 18, a second chill occurred. On November 1 he had a third violent chill. The temperature rose to 104° , he went into a coma for about thirty-six hours and showed Cheyne-Stokes breathing. During this attack a stubborn hiccough developed which lasted for about one week. At the time of this last chill, a questionable mass was felt in the left upper quadrant interpreted as being the spleen or the left kidney. There was also found a marked leukopenia, the white count falling to 2000 with marked relative lymphocytosis.

Throughout this period, numerous examinations and tests were carried out trying to explain the persistent troublesome pains in the legs and the attacks of chills, but without success. Blood cultures were negative, Roentgen rays of the chest and bones were negative, blood chemical studies were normal. Blood-urea nitrogen was 10 mg. per 100 cc. Phthalein test was 60 per cent. There were no signs of anemia. The urine was negative except for a rare white blood cell. General physical examination was entirely negative except for marked tenderness on pressure of both arms and to less extent of the legs. Patient was eating quite well and except for the pain was quite comfortable.

He was taken to the hospital for more careful observation of the genito-urinary tract. Roentgen rays of the kidney and pyelograms were negative. No organisms were found in the urine from either ureter. Numerous physicians had seen the patient and it was thought by some that prostatic obstruction might possibly be the cause of the trouble and that the mass felt by one observer in the left upper abdomen could have been an intermittent hydronephrotic kidney. Because of this a suprapubic prostatectomy was performed November 21. The day after the operation, the patient was comatose and showed Cheyne-Stokes breathing and a very distressing hiccough again developed and persisted for ten days. November 27 another severe chill occurred, the temperature rising to 103° . It returned to normal in thirty-six hours. Before this chill, the patient had cleared mentally but again became stuporous and irrational directly after the chill. All this time pains in the arms were very troublesome. On December 5, the fifth major chill occurred, the patient grew cold, began to shake and tremble all over. After about a half hour it was over and a semi-conscious state developed.

At this point, for the first time, definite and marked rigidity of the neck was noted. A lumbar puncture was performed and 10 cc. of slightly cloudy spinal fluid was removed. One hundred and seventy-six cells per cubic millimeter were found, practically all polymorphonuclear leukocytes. No organisms were found. During this chill and shortly after it several blood cultures and spinal fluid cultures were made in aseptic, hydrocele and dextrose broth. These and subsequent bacteriologic examinations were carried out by Prof. Hans Zinsser. Antimeningococcus serum was injected intraspinally (30 cc.) and intravenously (60 cc.). It was thought at this time that the patient may have had a meningococcemia during the past

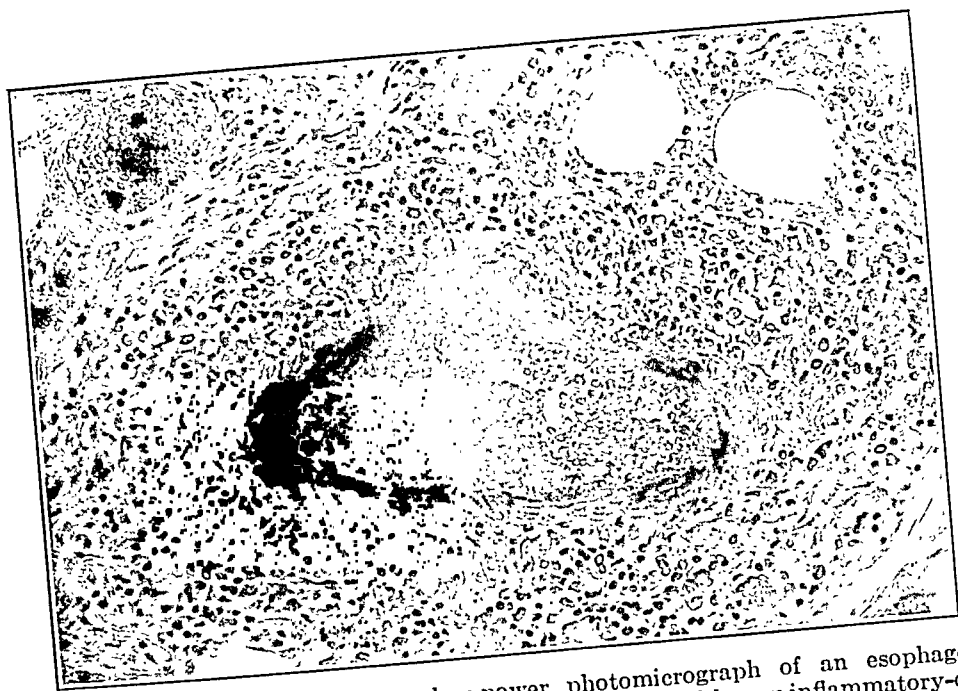


FIG. 2.—Case II. A medium low-power photomicrograph of an esophageal artery showing almost complete destruction of the wall and heavy inflammatory-cell infiltration.

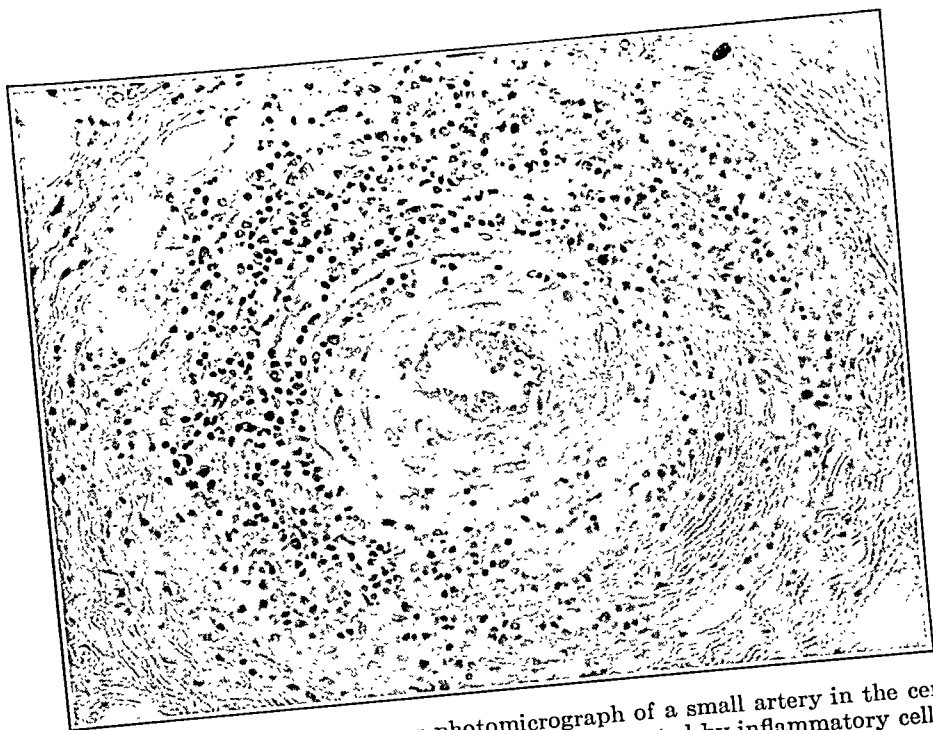


FIG. 3.—Case II. A low-power photomicrograph of a small artery in the center of the sciatic nerve, the wall of which is heavily infiltrated by inflammatory cells.



FIG. 4.—Case II. A low-power photomicrograph of pancreatic vessels which indicates the intimal proliferation with partial medial necrosis and heavy periarterial infiltration by a variety of inflammatory cells.

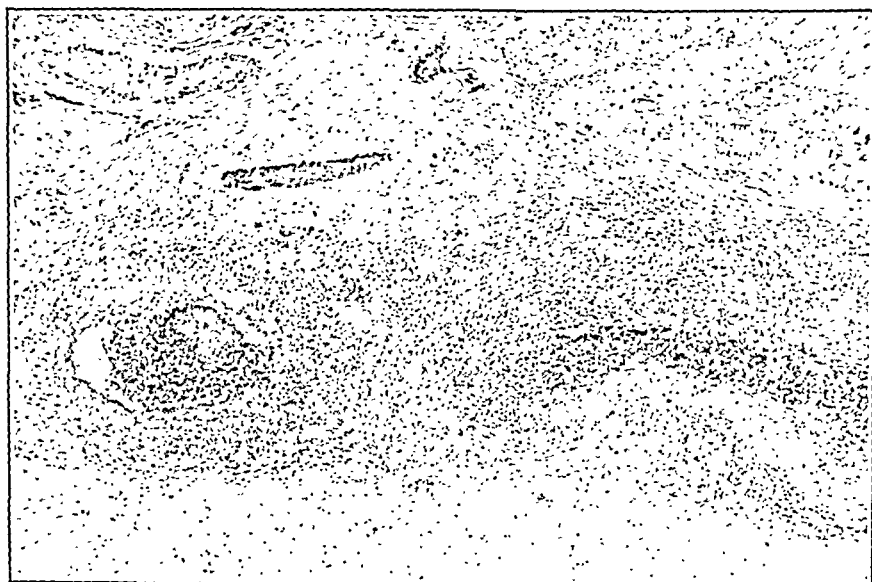


FIG. 5.—Case II. Low-power magnification showing extensive perivascular infiltration with proliferation of the endothelium of the intima and necrosis of the media, in the vessels of the testicle.

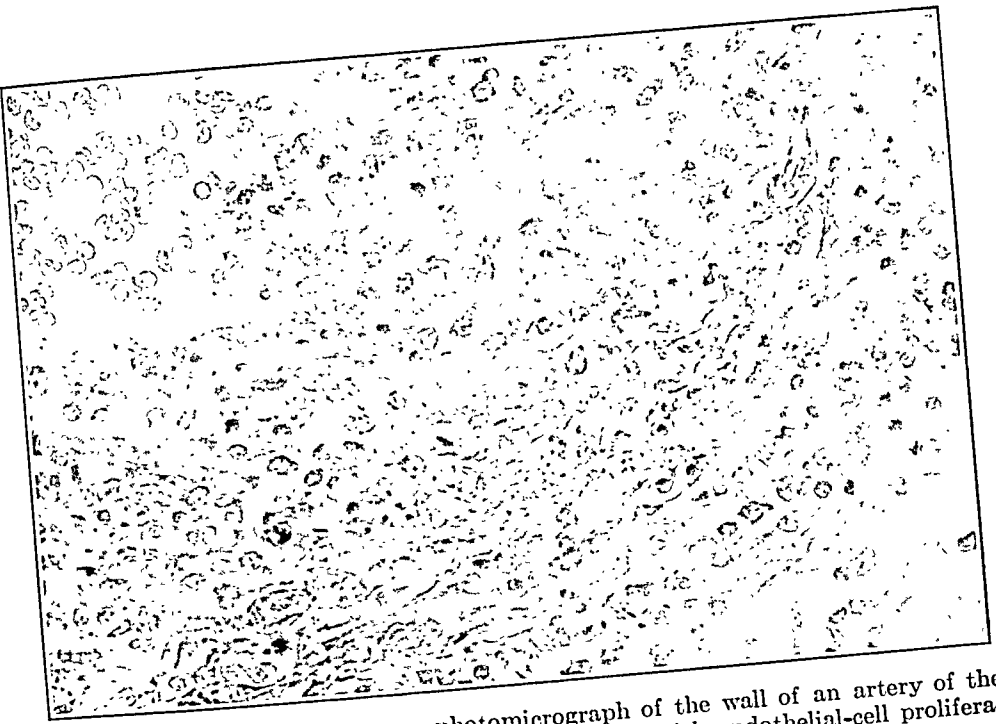


FIG. 6.—Case II. High-power photomicrograph of the wall of an artery of the testicle showing almost complete medial destruction with endothelial-cell proliferation into the lumen.

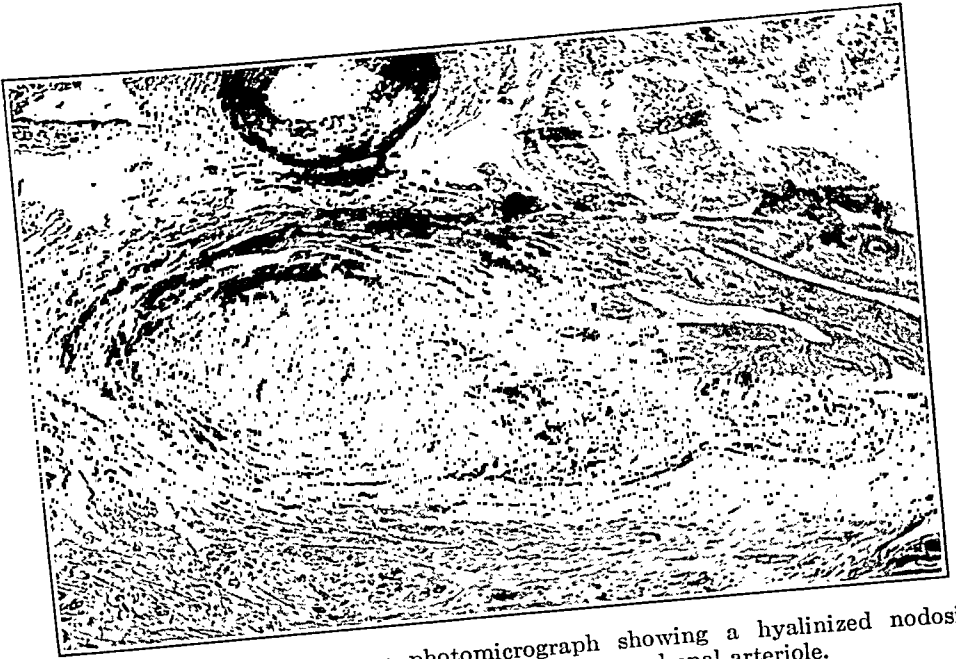


FIG. 7.—Case II. Low-power photomicrograph showing a hyalinized nodosity and inflammatory-cell infiltration in an adrenal arteriole.



FIG. 8.—Case II. Low-power magnification revealing the perivascular infiltration with some destruction of the vessel wall in the musculature of the urinary bladder.

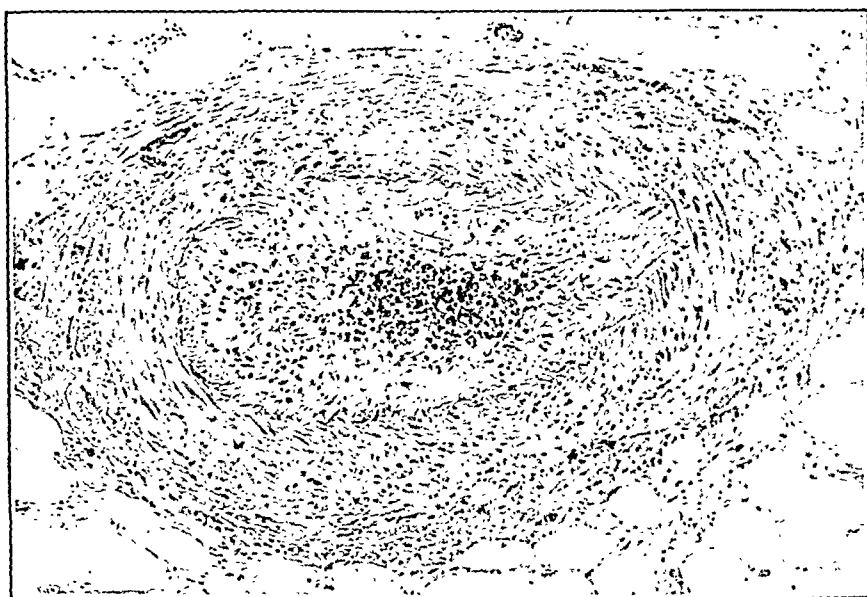


FIG. 9.—Case II. A small artery in the perivesical fat showing marked intimal thickening with relatively little inflammatory-cell infiltration.



FIG. 10.—Case II. Low-power photomicrograph showing two small pulmonary arteries containing partially organized thrombi.

four months, which finally terminated in meningitis. Three more similar treatments with serum were given both intraspinally and intravenously in the next few days. The cell counts in the spinal fluid were 800 on December 7, 350 on December 9 and 30 on December 19. No organisms were recovered in any of the bacterologic examinations. The temperature remained elevated and after five days gradually returned to normal. During this time the patient was unconscious but after the temperature returned to normal his mind became clearer although frequently he would lapse back into a disoriented state. There were no more chills after this. For a while he improved and began to eat and it seemed as if he would recover. However, he developed several bed sores as he was incontinent most of the time, a large abscess over the lower sacrum had to be incised, he gradually grew weaker, went into a coma and died peacefully January 1, 1928.

Some other points of interest might be mentioned. Blood smears were examined carefully for malaria parasites but none were found. White blood counts, which were frequently made, showed a slight leukocytosis most of the time, from 11,000 to 17,000, even when the patient was feeling fairly well and there were no chills. When the temperature was elevated, the white count was around 23,000. On December 19 the stained blood smear showed a normal number of platelets, but the differential white count showed 18 per cent transitional cells. Electrocardiograms were normal, the blood pressure was about 130 systolic, 80 diastolic. Wassermann test was negative.

Throughout the illness, a source of infection or a localized area of pus was sought for. All our examinations failed to show the cause of the disease. At one time the possibility of brain abscess came up. The ophthalmoscopic examination was negative and Dr. Cushing, who saw the patient in consultation, found no evidence of localized brain pathology. He was treated with antimeningococcus serum because it was barely possible that he was suffering from meningococcemia with terminal meningitis. It is quite definitely known that at times this diagnosis is almost impossible to establish and this treatment offered the hope of a cure if the diagnosis had been correct. The autopsy findings of periarteritis nodosa came as a complete surprise to all those who attended the patient.

Pathologic Report. A complete necropsy performed five and a half hours postmortem showed, in the gross, numerous large infarctions of both lungs, a moderately severe bronchopneumonia, some cystitis and a decubitus chronicus over the sacrum. Although a careful search was made, no lesions were found in the gross examination, to explain any of the patient's unusual symptoms. The long bones, vertebræ, sciatic and brachial nerves were examined and the brain and spinal cord were removed. It was not until the sections were examined microscopically that the true nature of the disease was understood.

Microscopic Description. The microscopic study of the tissues revealed, unexpectedly, a widespread vascular disease, with inflammatory lesions of especial interest in nearly all the organs of the body. These lesions were all very similar in that they all showed varying stages of tissue response to a presumably infectious agent, and that they were all confined to the blood-vessel walls and perivascular areas. In all instances the histopathology corresponded very closely to the vascular changes described in periarteritis nodosa. Because of the similarity of each lesion and the very complete descriptions given by other authors, only a brief report of the microscopic findings will be given.

Involved vessels show considerable variation in size but in most instances it was the small- and medium-sized arteries which showed the more extensive changes. While the principal cellular infiltration was external to the vessel walls, the walls themselves were often partially or completely de-

stroyed and there was a heavy infiltration with endothelial leukocytes, lymphocytes, polymorphonuclear leukocytes and fibroblasts. There was marked loss of cellular definition of the media coats as well as the heavy inflammatory cell infiltration. In many places the weakening of the wall was made evident by the marked necrosis of the media, which in places had reached such a degree that only a few hyalinized muscle fibers remained. A crescentic thickening of the intima due to an endothelial-cell proliferation was a notable feature in many instances; this also was accompanied by infiltration of polymorphonuclear leukocytes and lymphocytes. The intimal thickening was usually more pronounced on the side of most marked medial destruction. In a few of the older lesions, notably the lungs, an occasional organized and partially canalized thrombus was present. The inflammatory process in practically all instances extended out into the perivascular tissues and was characterized by an infiltration with endothelial phagocytes, lymphocytes, polymorphonuclear leukocytes and fibroblasts. Marked congestion in these areas was also frequently seen. Because of the dense cellular infiltration it was difficult to find the bloodvessels of the vasa vasorum, but the impression was frequently gained that there was new bloodvessel formation in the adventitia.

Special mention of the central and peripheral nervous system seems warranted in relation to the unusual symptomatic manifestations. Examination of sections from a great many blocks of brain, spinal cord and the brachial and sciatic nerves revealed scattered lesions of some of the included vessels. While the involved arteries were not as numerous nor as extensive as those in other parts of the body, they were in other respects similar and denoted a periarteritis as well as an arteritis and an endarteritis. Evidence of a healing or a healed meningitis could not be found in a study of numerous sections taken for that purpose.

Bacteriology Note. The bacteriology that was done consisted of cultures made from the heart's blood, spleen and meninges, using blood agar, hydrocele agar, and brain broth as culture media. All of the original cultures and subcultures were overgrown with colon bacilli, but no other organisms could be found. Sections from the more extensive lesions were made and stained by Gram's, Giemsa's, Goodpasture's and Levaditi's methods, but no organism nor spirochetes could be found. It must be noted that numerous cultures were made from the blood and spinal fluid during the height of fever and during the active stages of meningitis but no organisms were ever grown. These cultures were made in ascitic, hydrocele and dextrose broth.

Summary. The first case reported herein occurred in a young man, aged twenty-two years, and was typical of periarteritis nodosa. It belonged to the cardiorenal type of the disease for hypertension, cardiac and marked renal insufficiency were present. At autopsy, the nodosities along the medium sized arteries were recognized in the gross.

The second case was most unusual. There were repeated severe chills and fever (Fig. 1) with perfectly normal periods of about one week between these spells. Practically the only complaint and the one with which the illness was initiated was painful and tender limbs. This symptom persisted until the end. After a course of three months, clinical evidence of meningitis and coma developed. The spinal fluid findings with a high leukocyte count indicated an active meningitis, but no organisms could be cultured from either the blood or spinal fluid at any time, and no organisms were ever

found in smears. Because the clinical course was similar to the rare instances of meningococcemia with terminal meningitis, the patient was given antimeningococcic serum without any effect.

On postmortem examination typical microscopic lesions of periarteritis nodosa were found in the bloodvessels of almost all the organs of the body. Some of these lesions were acute in nature while others were in varying stages of healing, making the total picture compatible with the long clinical course of the disease. The coronary arteries were particularly spared and the arteries of the nerve trunks were markedly involved.

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REVIEWS.

BRONCHIAL ASTHMA. ITS DIAGNOSIS AND TREATMENT. By HARRY L. ALEXANDER, A.B., M.D., Associate Professor of Medicine in the Washington University Medical School, St. Louis; Associate Physician to the Barnes Hospital, St. Louis. Pp. 171; 8 illustrations. Philadelphia: Lea & Febiger, 1928. Price, \$2.25.

IN the last few years a number of books have been written on bronchial asthma. Their authors have usually fallen into the same errors: an overemphasis of the rôle of hypersensitiveness in the disease and the omission of much important older work. This is the first book in which these pitfalls have been successfully avoided. The author has managed unusually well to keep both feet on the ground in his correlation of the old with the new, so that he may well be forgiven his stand on a few minor controversial points, such, for example, as the inclusion of vaccines only under the head of "Non-specific Therapy." The reviewer does not hesitate to recommend this book to physicians and students as the best on the subject.

R. K.

GROWTH. By WILLIAM JACOB ROBBINS, SAMUEL BRODY, ALBERT GARLAND HOGAN, CLARENCE MARTIN JACKSON and CHARLES WILSON GREENE. Pp. 189; 83 illustrations. New Haven: Yale University Press, 1928. Price, \$3.00.

THE series of popular lectures published in this volume was delivered under the auspices of the Missouri Chapter of the Sigma Xi. Each of the five lectures was delivered by a member of the faculty of the University of Missouri.

W. J. Robbins gives the introductory chapter a clear and interesting discussion of growth in general. The course of growth and senescence is presented by Samuel Brody from the viewpoint of mathematical analysis. A. G. Hogan discusses the relations between growth and nutrition, giving timely information on the present status of vitamins and foodstuffs to growth. What determines bodily form is the subject of the chapter by C. M. Jackson. Finally the important subject of internal secretions in their relation to growth is presented by C. W. Greene.

Each of these contributors is a recognized authority in his field.

While the matter is presented in a way comprehensible even to the nonmedical reader, it should be chiefly valuable to the physician who wishes to bring up to date his knowledge on this very vital subject.

M. M.

WILLIAM HARVEY, By ARCHIBALD MALLOCH, M.D. (McGILL), M.R.C.P. (LOND.), Librarian, New York Academy of Medicine. Pp. 103; 13 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$150.

TERCENTENARY editions of Harvey's works have already been reviewed in these columns; and now we have, in the attractive form and low price that we have come to expect and appreciate in Hoeber's Biographical Series, a short life based on the author's tercentenary address at Boston. In addition to the briefly told story of the discovery of the circulation, one reads interesting comments on Harvey's continental tours, his intercourse with the witches, his autopsy of "Old Parr," his connection with the College of Physicians and of his other great work, "*de Generatione Animalium*." This booklet will not, and is not intended to, replace the longer lives by Willis, Power and others.

E. K.

HANDBOOK OF MICROSCOPICAL TECHNIQUE. EDITED By C. E. McCLUNG, PH.D., Professor of Zoölogy and Director, Zoölogical Laboratory, University of Pennsylvania. Pp. 495; 43 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$8.00.

A DESIRABLE supplement to the volumes of General and Special Cytology, the latter from the same publisher—an association that is emphasized by a similarity of binding—this handbook aims to present precise details of technique of the methods involved.

The short first part, by Doctor McClung outlines for the inexperienced worker approved general methods of preparing microscopical slides. Part two discusses in more detail the following special methods: Microdissection, by R. Chambers; Vital Stains, by N. C. Foot and F. R. Sabin; Bacteriological Methods, by H. J. Conn, F. B. Mallory and F. Parker, Jr.; Botanical Microtechnique, by W. R. Taylor and S. H. Eckerson; Cytological Methods, by C. E. McClung, E. Allen, R. T. Hance, J. W. McNabb and E. V. Cowdry; Embryological Methods, by C. E. McClung and E. Allen; Red Blood Cells, by R. Isaacs; Leukocytes, by E. M. Slider and Hal Downey; Bone, by Paul G. Shipley; Dental Technique, by J. L. T. Appleton, Jr.; Intercellular Substances of the Connective Tissues, by F. B. Mallory and F. Parker, Jr.; Muscle and Electric Organ Tissues, by U. Dahlgren; Neurological Technique, by W. H. F.

Addison, W. Penfield and W. V. Cone; Protozoölogical Methods, by D. H. Wenrich; Fixation and Fixatives, by C. E. McClung and E. Allen; Stains by C. E. McClung and H. J. Conn.

Thus it will seem that the eminence of these contributors guarantees the editor's assumption that the work will be "of interest to workers in bacteriology, botany, cytology, embryology, histology and pathology" and of practical use as well. Where all parts are good, distinctions are especially invidious, but one cannot help but call attention to the sections on microdissection, vital staining, intercellular tissues, and the newer neurological methods, if only for the added convenience that this presentation offers. Overlapping perhaps the field of such books as Lee's "Microtometist's Vademecum" and Mallory and Wright's "Pathological Technique," this book covers a number of topics not included in other works and will be correspondingly welcome. It is difficult to see how it can be omitted from the bookshelf of any biological laboratory or student earnestly concerned with these subjects.

E. K.

HISTORY OF MEDICINE. By FIELDING H. GARRISON, M.D., Lt.-Col., M.C., U.S. Army. Fourth edition. Pp. 996; 286 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$12.00.

A NEW edition of this best of all histories of medicine is an important event in medical publishing, and especially so when it has been as carefully and extensively revised as is here the case. A melancholy flavor is added by the author's acknowledgements *zum letzten mal*, but let us hope that as with other artists, operatic and otherwise, circumstances may prove too strong for him.

As compared with earlier editions the book has been somewhat enlarged, but kept within convenient bounds by the use of a slightly enlarged page and smaller font in places and by curtailing the earlier phases to permit a more adequate presentation of the constantly growing "modern" section. Colonel Garrison's specialization in this field peculiarly fits him to do justice to this most difficult of all periods and in spite of the fuller treatment, it is safe to say that its inherent worth could justify an even greater number of pages. The lessons and medical achievements of the World War have been included, also a new chapter on prehistoric medicine, and the Appendiceal Chronologic list and Bibliographic Notes considerably extended. In the newly-written preface one finds an interesting survey of the increasing interest in medical history since the publication of the third edition seven years ago. The author seems to have demonstrated that occasionally it is possible profitably to gild the lily.

E. K.

THE STORY OF MODERN PREVENTIVE MEDICINE. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 295; 9 illustrations. Baltimore: Williams and Wilkins Company, 1929.

THIS volume is a continuation of "Evolution of Preventive Medicine" (1927), which described the subject up to the time of Pasteur. It nevertheless tells a united story of the topics it deals with, so that Laennec, Villemin and others appear in the chapter on causation of diseases; Leeuwenhoek and Redi in the settling of the question of spontaneous generation and so on. We are carried in twenty-nine chapters through all the infectious diseases, then through historical considerations of physical and social conditions of health (ventilation, sunlight, housing, etc.) and finally through some physiological conditions of health, such as goiter, hormones, vitamins and alcoholism.

Written by an acknowledged expert in this field, the description of the progress in our knowledge of the cause, prevention and cure of these diseases may be taken as authoritative. As the treatment is elementary, much will be found by the educated physician that is not new to him, but much more which is both interesting historically and important practically.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

Report on Fourth International Congress of Military Medicine and Pharmacy, Warsaw, Poland. May-June, 1927. By WILLIAM SEAMAN BAINBRIDGE, COM., M.C., U.S.N.R. Pp. 248; illustrated. Menasha, Wis.: Collegiate Press, 1929.

*Nephritis: Its Problems and Treatment.** By T. IZOD BENNETT, M.D. (LOND.), F.R.C.P. Pp. 94; 3 illustrations. New York: Oxford University Press, American Branch, 1929.

Youthful Old Age. By WALTER M. GALLICHAN. Pp. 236. New York: The Macmillan Company, 1929. Price, \$2.50.

A book by a layman who has apparently attained the philosophy of Rabbi Ben Ezra, and says that he is happier at sixty-seven than he was at thirty years. Those who agree with the author that "life is a sweet potion of labor and love and life is worth living" should be interested.

Endocrine Diagnostic Charts. By HENRY R. HARROWER, M.D. Pp. 144. Los Angeles: The Harrower Laboratories, Inc., 1929. Price, \$1.00.

*Antenatal Care.** By W. F. T. HAULTAIN, O.B.E., M.C., B.A., M.B. (CAMB.), and E. CHALMERS FAHMY, M.B. (EDIN.), F.R.C.S.E. Pp. 113. New York: William Wood & Co., 1929. Price, \$2.25.

*The Normal and Pathological Physiology of Bone: Its Problems.** By R. LERICHE and A. POLICARD. Pp. 236; 33 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, \$5.00.

*The Climacteric.** By GREGORIO MARANON. Pp. 425; 19 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$6.50.

* Reviews followed by an asterisk will appear in a later number.

*Oxford Monographs on Diagnosis and Treatment. Volume I: Disorders of Metabolism.** By JAMES S. MCLESTER, M.D. Edited by HENRY A. CHRISTIAN, M.D. Pp. 328. New York Oxford University Press, American Branch, 1929. Price, \$100, a set of 10 volumes.

*Volume II: Diseases of the Stomach and Intestines.** By WILLIAM FITCH CHENEY, B.L., M.D. Pp. 280.

*Volume III: The Diagnosis and Treatment of Diseases of the Heart.** By HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Pp. 355.

*Volume IV: The Diagnosis and Treatment of Diseases of the Thyroid.** By JAMES H. MEANS, M.D., and EDWARD P. RICHARDSON, M.D. Pp. 366; 50 illustrations.

Progressive Medicine. Volume I, March, 1929. Edited by HOBART AMORY HARE, M.D. Pp. 352; illustrated. Philadelphia: Lea & Febiger, 1929.

*Injection Treatment of Internal Hemorrhoids.** By MARION C. PRUITT, M.D., L.R.C.P.S. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S. Pp. 137; 9 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$3.00.

Medical Information in Sickness and Health. By PHILIP SKRAINKA, M.D. Pp. 577. Coward-McCann, Inc., 1929.

A book on household medicine calculated "to bring doctor and patient closer together." The historical notes that introduce some of the diseases are of especial interest.

*The Newborn Infant.** By EMERSON L. STONE, M.D. Pp. 183. Philadelphia: Lea & Febiger, 1929. Price, \$2.00.

Surgical Clinics of North America. Chicago Number, April, 1929, Volume IX, No. 2. Pp. 243. Philadelphia: W. B. Saunders Company, 1929.

*An Index of Symptomatology.** By Various Writers. Edited by H. LETHBY TIDY, M.A., M.D. (OXON.), F.R.C.P. (LOND.). Pp. 710; 130 illustrations. New York: William Wood & Co., 1929. Price, \$12.00.

Gleanings from General Practice. By DAVID TINDAL, M.D., F.R.F.P.S. (GLAS.). Pp. 209; 3 illustrations. New York: William Wood & Co., 1929. Price, \$2.50.

Tips gleaned from a long clinical experience, calculated to be of use to the young practitioner. Chiefly concerned with medical treatment.

Transactions of the American Surgical Association. Volume XLVI, 1928. Edited by JOHN H. JOPSON, M.D. Pp. 503; illustrated. Philadelphia: J. B. Lippincott Company, 1929.

*Clinical Electrocardiograms: Their Interpretation and Significance.** By FREDERICK A. WILLIUS, M.D. Pp. 219; 368 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$8.00.

NEW EDITIONS.

The Writing of Medical Papers. By MAUD H. MELLISH-WILSON, Editor of Mayo Clinic. Third edition. Pp. 184. Philadelphia: W. B. Saunders Company, 1929. Price, \$1.50.

A booklet that should be on the desk of everyone writing a medical paper. If, in addition, its precepts could be carried out, even to a 50 per cent extent, the lives of medical editors would be considerably lengthened.

Tuberculosis and How to Combat It. By FRANCIS M. POTTENGER, A.M., M.D., LL.D., F.A.C.P. Pp. 275. Second edition. St. Louis: C. V. Mosby Company, 1929. Price, \$2.00.

* Reviews followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Splenic Lesion in Sickle-cell Anemia.—RICH (*Bull. Johns Hopkins Hosp.*, 1928, 43, 398) found five such characteristic lesions in the spleens of Sickle that he was able to pick out of 5000 autopsied spleens 62 which showed the same change. Further investigations showed that all these were from negroes and sickle cells were found in all. The lesion is a congenital malformation of the splenic sinuses which permits an excessive escape of red cells into the pulp. Pronounced malformation of the spleen about the Malpighian follicles causes a collection of pools of blood in these areas which later become greatly fibrosed and perhaps calcified, resulting in marked atrophy. The anemia is of a hemolytic type with a development of hemosiderin in the tissues.

Xanthomatosis and the Reticulo-endothelial System.—An important correlation of a group of cases of Christian's syndrome (defects in membranous bones, exophthalmos and diabetes insipidus) has been made by ROWLAND (*Arch. Int. Med.*, 1928, 42, 611), on the basis of 2 original cases and 12 in the literature occurring in early childhood. He draws certain conclusions as to their microscopic changes, pathogenesis and their relation to the reticulo-endothelial system. There was a generalized visceral xanthomatosis in which many parts of the system show storage, or diffuse hyperplasia in various organs, particularly the bone marrow, lymph nodes and spleen. He considers that lipoids and other substances in the body fluids, becoming pathogenic, irritate the vessel walls with perivascular cell infiltration; the lesions increasing as a result of the progressive blockage of the system with compensatory hyperplasia in an attempt to get rid of the harmful substances. Abnormal congenital pre-disposition has not been proved. He finds no essen-

tial difference between all the forms of xanthoma and Gaucher's and Niemann's disease. The above distribution, exophthalmos, diabetes insipidus, dwarfism and infantilism, are all the result of this pathogenic change acting through the pituitary.

Relation of the Bone Marrow to Disease.—In 130 autopsies in which the bone marrow was examined, STAAL (*Inaug. Diss., Groningen, 1927*) found that changes first took place in the lower epiphysis, and that the red marrow peristed longest in the upper part of the diaphysis and shaft. In inflammations active hyperemia may appear as soon as two days, to be quickly followed by increase of myeloid tissue and atrophy of the fat cells. Lymphocytic changes are only found in lymphadenoma, but status lymphaticus is not a prerequisite for the presence of lymph follicles. Tumors in the aged are most apt to produce gelatinous degeneration, which also may occur in the cachexia of acute and chronic inflammations. The most marked change occurs in the so-called primary blood diseases and in extensive carcinomatous metastasis or myelophthisis.

Hypercholesterolemic Splenomegaly.—An interesting case exhibiting subacute hypertrophic biliary sclerosis with icterus and hypercholesterolemia (1250 mg. per 100 cc.), xanthoma and splenomegaly is reported by DYKE (*J. Path. and Bact., 1928, 31, 173*). Both splenomegaly and the xanthomata were considered to be the result of the high cholesterol content of the blood.

SURGERY

UNDER THE CHARGE OF

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Dupuytren's Contraction.—KANAVEL, KOCH and MASON (*Surg., Gynec. and Obst., 1929, 48, 145*) say that twenty-nine cases of Dupuytren's contraction are reported which have served as an incentive for a careful study of the normal fascia of the hand and an opportunity for observing the unusual changes which it undergoes in this condition. Seven of these cases had been operated upon previously, some of them more than once and in each case the condition had recurred. The results observed in such cases and the results obtained in the cases operated upon by the authors have impressed them with the importance of wide excision of all the fascial attachments to the skin, to the interfascial septa and to the phalanges. Although in such an operation apparently normal fascia may be removed, these authors do not consider this a disadvantage, but rather an added guarantee against recurrence. Careful dissection and elevation of the skin is done to

avoid trauma and subsequent necrosis. Painstaking effort is taken to avoid injury or division of the digital nerves and bloodvessels which are frequently embedded in the bands of fibrous tissue which draw the fingers into flexion. Skin that is hopelessly involved is excised and replaced by a free full-thickness graft. In long-standing cases with marked contraction of the fingers, the head of the proximal phalanx is excised and the extensor tendon is shortened through a dorsal incision. Active movement of the fingers and hand are followed as soon as the operative wound is soundly healed.

Primary Carcinoma of Lung.—KIRKLIN, PATERSON and VENSON (*Surg., Gynec. and Obst.*, 1929, 48, 191) declare that in the early stages carcinoma of the lung may be divided into two types with clinical and roentgenological entities: Bronchial, arising in the wall of a first to third degree bronchus, and parenchymal, arising in the substance of the lung. In the bronchial type there is a history of early chronic, persistent cough, not greatly productive, but often associated with hemoptysis or blood-tinged sputum. Usually there is a loss of weight. Unilateral infiltrating density at the hilum is seen in the roentgenogram in some cases, but more constantly atelectasis of a lobe, due to bronchial obstruction is seen. The parenchymal tumor is more latent, but there is definite loss of weight and a peculiarly ill-localized type of pain in the chest. Later the bronchus may become invaded, in which case the lesion resembles the bronchial group. In the roentgenogram it is seen as a round nodule, with infiltrating edges and lying free in the lung tissue. Later it involves the whole or most of a lobe. In the later stages the two types tend to a common type and the actual malignancy is obscured either by pleural effusion or by infective processes. This is associated with dyspnea or the usual evidences of infection. Pathologically the analysis seems to show that the parenchymal tumor is usually an adenocarcinoma, that the bronchial tumor may be either adenocarcinoma or epithelioma, the epithelioma being confined to the bronchus and the lesion is of a high grade of malignancy.

Strangulated Left Duodenal Hernia.—COLEY (*Arch. Surg.*, 1929, 18, 868) finds that the retroperitoneal hernia is a relatively rare condition, since only 38 reported cases of all types were found by Short in a ten-year period. Hernia into the left paraduodenal fossa is by far the most common variety of retroperitoneal hernia. Forty-three cases of left paraduodenal hernia, which produced symptoms during life, were reported by Short in 1925. The author has added 7 more cases and reported an eighth, bringing the total number to 51. The symptoms are, for the most part, those of intestinal obstruction, but the presence of a mass to the left of the median line is important. Diagnosis is seldom made before operation. Treatment consists in reduction of the herniated intestine, with care to avoid injuring the vessel, which lies in the free edge of the neck of the sac. Partial excision of the sac or obliteration of its cavity, is advisable whenever possible. The condition of the bowel may necessitate resection. The mortality rate after operation has been decreasing. This may be attributed, in part, to more prompt surgical intervention in cases presenting symptoms of intestinal obstruction.

Cholecystogastrostomy—An Experimental Study.—BEAVER (*Arch. Surg.*, 1929, 18, 899) states that an experimental study of cholecystogastrostomy was undertaken to determine the effect of bile in the stomach on gastric secretion and mobility as well as the possibility of the biliary tract and liver. Twelve normal dogs were studied in two series of six dogs each. In the first series gastric digestion was studied by the McCann method of fractional gastric analysis for dogs. The emptying time of the stomach was also determined by means of the barium meal and the fluoroscope. Cholecystogastrostomy was then performed with double ligation and incision of the common bile duct. Following recovery fractional gastric analyses were again made to determine whether the bile had any effect on gastric acidity. The results in the first series showed definitely that bile did not have any effect on the acidity of the stomach. The postoperative emptying time was essentially the same as the preoperative. In the second series of dogs gastric analyses were not made, but the same type of operation was performed as in the first series. The dogs were allowed to live under normal conditions for varying lengths of time and were then operated upon to determine whether pathologic processes were developing in the gall bladder and liver. The results of the observations in the second series led to the conclusion that infections of the biliary tract and liver always occur following cholecystogastrostomy. It is suggested that the absence of clinical evidence of such infections does not preclude the possibility that pathologic changes in the biliary tracts and liver are occurring in patients subjected to cholecystogastrostomy.

THERAPEUTICS

UNDER THE CHARGE OF

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Liver Diet and Funicular Myelosis.—WOLF (*Med. Klin.*, 1928, 24, 1673) records a case of well-developed posterior lateral column myelosis in a patient suffering from a moderate grade of pernicious anemia in whom the administration of a diet containing 300 gm. of liver per day brought about a complete restoration of the blood picture and a very pronounced improvement in the nervous manifestations. Hearing, ataxia and paresthesia were all greatly benefited by the treatment and the objective signs on the part of the nervous system disappeared almost entirely. He cites a second patient in whom some improvement in the blood picture has already been produced but in whom the treatment has not been sufficiently prolonged to determine whether or not it may be capable of overcoming the symptoms of myelosis although some improvement has been observed within the first two weeks of treatment.

The close relationship known to exist between this form of myelosis and pernicious anemia seems to be further established by the response of the former, as well as of the latter, to the administration of liver.

The Use of Galvanocautery for the Destruction of Pleural Adhesions as a Preparation for Artificial Pneumothorax.—The use of artificial pneumothorax in the treatment of pulmonary tuberculosis is frequently rendered unsatisfactory or impossible by the presence of pleural adhesions which prevent satisfactory collapse of the lung. JACOBÆUS (*Therap. d. Gegen.*, 1928, 69, 433) advocates the severance of pleural adhesions by means of the galvanocautery for the release of the adherent lung as a preparation to the employment of pneumothorax. He states that the procedure is usually one that may be carried out without undue difficulty. The patient is studied by means of Roentgen ray in order to localize the adhesions. Then a thoracoscope is introduced under local anesthesia at a point usually from one to three intercostal spaces below the level of the adhesions. When the adhesions have then been studied visually through this instrument and accurately located a second thoracoscopic cannula is introduced to permit the passage of a galvanocautery. Under constant direct vision the adhesions are then slowly burned through. Experience shows that the results are more satisfactory and the danger of hemorrhage and subsequent spontaneous pneumothorax are much less when the cautery is used at a temperature just sufficient to cause it to glow a dull red. Extensive adhesions should be burned through at a point as far away from the lung as possible. From the author's experience in 150 cases he says that cordlike adhesion up to the thickness of the little finger can always be severed without much danger; that the same is generally true of membranous adhesions. Great care must be used, however, in the severance of large flat adhesions and it is best here only to burn through the granulation tissue which attaches the lung to the chest wall. In many such cases complete severance can be accomplished only by means of several successive operations. The operation is associated with certain complications most of which are, however, not serious. Subcutaneous emphysema is very frequent about the site of puncture. This lasts only two or three days and produces no ill effects. The operation is followed by pleural exudation in a considerable proportion of cases, some of which go on to the development of empyema. The majority of the exudates, however, are rather small and are usually absorbed within one to two weeks. In his series, he was able to complete the operation in a technically satisfactory manner in 121 out of the total 150 cases. Of these, the results were clinically satisfactory in 99. The most satisfactory clinical results are obtained in patients having cordlike and membranous adhesions located laterally. The next most satisfactory group is that with similar adhesions about the apex. Other forms and locations give results of somewhat doubtful value.

The Significance of the Liver Diet in Pernicious Anemia.—ARON (*Med. Klin.*, 1928, 24, 1696) directs attention to the fact that certain of the very severe anemias of childhood, such as the normoblastic anemia of von Jaksch, are nearly identical in many of their characteristics with pernicious anemia of the adult. He emphasizes the fact long known to pediatricists that these forms of anemia can be cured only

by dietetic methods. The effective diets are limited to those especially selected for their extreme richness in vitamin content, thus indicating that these forms of anemia probably rest upon a basis of vitamin deficiency. Intermediate between the juvenile anemias and pernicious anemia is the condition of tropical sprue in which the anemia resembles closely both the juvenile and the adult pernicious types and to which there is also added a group of symptoms somewhat analogous to those found in scurvy. This condition is also responsive only to the use of vitamin-rich diets. The author points out further the fact that the mammalian liver constitutes the chief reservoir for the storage and for the gradual release to the body of all three of the important vitamins. The liver is, in fact, more richly supplied with vitamins than any other food substance known. On the basis of this fact and of the analogies between the infantile anemia and sprue on the one hand and pernicious anemia on the other, the author suggests that the reason for the extraordinary therapeutic activity of liver and liver extracts in pernicious anemia is due to its high content of vitamins. He suggests that the highly specific value of liver and liver extract in pernicious anemia establishes this disease also among those due to vitamin deficiency. The failure of other methods of dietotherapy to relieve pernicious anemia is, in his opinion, due largely to the difficulty of introducing a sufficient quantity of the necessary vitamins in the form of the usual foodstuffs owing to their great bulk. It has been shown already that it is necessary to feed large quantities of the extraordinarily rich liver in order to control the disease. It seems probable, therefore, that once the disease is established its cure can be brought about only by the use of extremely large quantities of vitamins, such as has been proved to be the case with the juvenile anemias and with sprue. The suggestion is further made that by the administration of approximately equal amounts of the vitamins A, B and C, as obtained from other sources than liver, one should also be able to cure pernicious anemia. Up to the present time, however, no thoroughly adequate experiments have been made along these lines. The need in all of these forms of anemia for the administration of very large quantities of vitamins suggests that they are associated with: (1) Impaired absorption or increased destruction of the vitamins in the intestinal tract; (2) increased vitamin consumption due to infection; or (3) increased vitamin need through disturbances in the activity of internal secretions.

Contrasting sharply with the foregoing viewpoints is that of PONTICACCIA and CAMPANACCI (*Klin. Wchnschr.*, 1928, 7, 2153), who contend on the basis of their personal observations that the chief action manifested by liver, by which it brings about the rapid control of pernicious anemia, is due to its capacity to check the hemolytic destruction of the red cells. In their opinion this prompt antihemolytic action accounts for the immediate improvement in the general condition of patients with pernicious anemia which occurs before there are any evidences of change in the blood picture. Their contention seems further established by the prompt diminution in the content of bilirubin in both blood and urine and by the rapid increase in the cholesterolin content of the blood to supernormal levels. They believe that the changes in the bone marrow characteristic of pernicious anemia are not of fundamental importance, but are strictly secondary to disturbances in its function which follow as a result of pronounced hemolysis.

PEDIATRICS

UNDER THE CHARGE OF

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The Treatment of Rickets with Irradiated Ergosterol.—WILKES, FOLLETT and MARPLES (*Am. J. Dis. Child.*, 1929, 37, 483) treated 24 infants with rickets varying from mild to severe with irradiated ergosterol. Two babies with tetany were cured by the use of irradiated ergosterol. The irradiated ergosterol is in the form of a commercial preparation and was well taken and well tolerated. Two of the patients to whom it was given had severe bronchopneumonia and in several others cod-liver oil administration had been attempted but it had been refused or vomited. In their observations, they confirm the reports of other authors who had used irradiated ergosterol. They found that this preparation requires about three weeks to cause serum blood phosphorus and calcium concentration to return to normal. They also found that it required about the same time for the Roentgen ray signs of the healing of the rickets to appear and it further required about six weeks to obtain complete healing. These averages compare favorably with those obtained from the use of cod-liver oil, quartz light and eggs. Craniotabes was healed within an average period of one month in a series of 12 patients. Healing of the rachitic bone took place in one patient who had bronchopneumonia in spite of a low serum phosphorus and a calcium product of 20.5 mg. per 100 cc. They caution against using irradiated ergosterol in patients with tetany who show a high blood-phosphorus content. They believe that irradiated ergosterol is not a perfect preventative to rickets. They observed craniotabes developing in one patient who had received prophylactic doses of irradiated ergosterol although this lesion healed promptly when the irradiated ergosterol was continued in unchanged amounts.

Intraperitoneal Blood Transfusion.—COLE and MONTGOMERY (*Am. J. Dis. Child.*, 1929, 37, 497) claim that satisfactory therapeutic result is obtained by the intraperitoneal method as could be expected by the intravenous. In their 237 transfusions in 117 patients, reactions occurred in less than 7 per cent of the cases and in only 2 or 3 instances were they of noticeable importance. These reactions usually consisted of restlessness and of abdominal discomfort but were rarely accompanied by fever. Properly citrating the blood prevents these reactions. As these transfusions were all performed in private practice in nearly every case, the parents were the judges of the reactions which is fairly good evidence that they were slight. It is certain that the marked reactions which are rather commonly seen in the intravenous method occur much less often after intraperitoneal transfusions. In their entire series there were no evidence of injury to any abdominal organ nor have they ever experienced anything which could be regarded in any way as an unfavorable effect for the intraperitoneal injection. Of their series 20 patients

died and 3 came to autopsy. In one case some unabsorbed blood was found in the abdominal cavity but this patient was dying when the transfusion was given. The small amount of disturbance to the patient from the intraperitoneal transfusion is worthy of consideration. The struggling and crying incident to intravenous transfusion is often very harmful. The contraindications for intraperitoneal transfusion are the same as for any other type of transfusion with the addition that it should never be used where there is any question of intraabdominal disease or where even temporary abdominal discomfort might be a disadvantage, such as in severe cardiac disease or acute pneumonia. The use of citrated blood intraperitoneally has little use in the rapid replacement of blood volume in shock or hemorrhage and the hemostatic effect is probably delayed. In every other respect it possesses all of the advantages of intravenous transfusion with reduced reaction and easy administration.

An Experimental Study of the Use of Unsweetened Evaporated Milk for the Preparation of Infant Formulæ.—MARRIOTT and SCHOENTHAL (*Arch. Pediat.*, 1929, 46, 135) discuss the suitability of unsweetened evaporated milk in the preparation of infant-feeding formulæ. This product was fed to 752 young infants. A series of 670 infants either breast fed or fed on other milk modifications was used as a comparison. In the series fed on evaporated milk there were 570 newborn babies, 107 young infants in dispensary and private practice and 75 infants ill in hospitals. Eleven infants were premature. It was found that a larger percentage of the newborn babies regained the birth weight by the end of fourteen days when on formulæ prepared from evaporated milk than those fed exclusively on the breast or given other supplementary formulæ. The average daily gain in weight of the babies fed on formulæ prepared from evaporated milk was exactly equal to that of babies fed exclusively on breast milk or on formulæ prepared from bottled pasteurized milk. A group of sick infants made an average daily gain on evaporated milk formulæ which was somewhat better than that of a group of control infants fed by other methods who were also in a hospital during a period of observation. It was observed that the premature infants made especially good gains when fed on evaporated milk. As the result of their observations the authors feel that unsweetened evaporated milk from the nutritional standpoint is the full equivalent of pasteurized or boiled whole cows' milk. The continued use of evaporated milk as routine food for normal babies is not attended by nutritional disorders. It was found to be especially suitable for premature babies. It was found that evaporated milk when suitably modified was a satisfactory food for sick infants especially those suffering from nutritional or gastrointestinal disorders. The distinct advantages which recommend evaporated milk for general use are its sterility, its ready digestibility and its uniformity of composition.

The Early Diagnosis of Pertussis.—ORGEL (*Arch. Pediat.*, 1929, 46, 149) made observations on the intradermal reactions using several different pertussis vaccines. Using a vaccine containing 3000 million bacilli per cc. he obtained positive intradermal reactions 81 per cent of all the children tested and he found that the percentage of reactions

increased with the concentration of the vaccine. Using a vaccine containing 2000 million bacilli per cc. he obtained reactions in 50 per cent of all children but in 80 per cent of those children having pertussis and in 49 per cent of children that had previously had pertussis. Pertussis vaccines in concentrations less than 2000 million bacilli per cc. rarely caused positive intradermal reaction regardless of whether or not the child was suffering with pertussis. Other vaccines if containing 2000 million or more organisms per cubic centimeter cause positive intradermal skin reactions. Aolan did not cause any reactions in the children tested in this series. Colon bacillus vaccines in a dilution as low as 400 million bacilli per cc. gave positive intradermal reactions in all the cases tested. The author feels that a positive intradermal skin reaction obtained by the use of bacillus pertussis vaccine containing 2000 million bacilli per cc. is not diagnostic of pertussis.

The Leukocyte Count in Epilepsy.—PATTERSON and WEINGROW (*Arch. Neurol. and Psychiat.*, 1929, 21, 412) in studying 182 cases of epilepsy found 50 per cent showing an increase over the normal in the total white cell count, while in 20 per cent the count fell below normal. The leukocytosis which they observed was not neutrophilic but lymphocytic. Different evidences of epileptic leukocytosis being influenced by digestion of food was not observed. Within the limits of physiologic variation, the rise in the leukocyte count is the same in nonidiopathic as in idiopathic epilepsy. It seems that the leukocytosis frequently met in epilepsy is not due to the disease itself but to some associated phenomena. A connection between the leukocyte count in epilepsy and the presence or absence of an aura apparently does not exist. No relationship could be shown between onset and duration and the white cell count nor does the leukocyte count in epilepsy seem to be affected by the secondary anemia which often accompanies the disease.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Lipid Studies in Xanthoma.—WILE, ECKSTEIN and CUTIS (*Arch. Dermat. and Syphilol.*, 1929, 19, 35) find that xanthoma, long considered to be a cholesterol-containing tumor of the skin, contains in reality very little cholesterol, and considerable amounts of other lipids. In several cases a rapid clinical response with involution of the tumors was produced by placing the patients on a reduction diet, as for obesity.

The authors believe that the cholesteremia usually observed in these patients and the formation of the lipid tumors are both expressions of an underlying disturbance of fat metabolism, possibly of central origin.

Hemotogenous Production of Dermatomycoses.—FRIED and SEGAL (*Arch. Dermatol. and Syphilol.*, 1929, 19, 98) find that in confirmation of the results of Saeves, intravenously injected suspensions of *Trichophyton* organisms localize in the skin of animals only if there has been a certain degree of capillary injury such as is produced by shaving. The trauma to the vessels permits the fungus in the circulation to "leak through," producing lesions only in the skin. The intravenously introduced parasite circulates in the blood for not less than three days.

Experimental Urticaria Factitia.—WALZER, *Arch. Dermatol. and Syph.*, 1928, 18, 868) found that injection of the serum of dermatographic subjects into the skins of normal persons did not transmit to the normals the capacity for developing wheals on trauma to the injected sites, except in the case of the serum of a single patient, with a papular dermatosis which the author was unable to diagnose, but which apparently had an urticarial phase. Following the injection of this patient's serum into their skins, 7 of 12 normal subjects reacted to stroke or other mechanical trauma at the site of injection with the production of wheals. The author is convinced that the transferred substance which brings about wheal formation in normal subjects, is not histamin as described by Lewis. In the discussion it was suggested that the substance might be tyramin, recently recognized in the circulation of some subjects.

The Elimination of Bismuth from the Human Organism.—ENGELHARDT (*Arch. f. Dermatol. u. Syphilol.*, 1928, 156, 1). This is a 40-page summary of studies of the elimination of bismuth as tested with several types of preparations, by oral, inunction, intravenous and soluble and insoluble intramuscular injections in aqueous and oily suspensions. Only the principles which have therapeutic application are here cited. A slight but unimportant elimination of bismuth follows administration by mouth and inunction. The elimination is rapid following intravenous injection. This fact, together with the necessarily more frequent injection, the great toxicity, and the needlessness of excessively rapid bismuth effect as a spirillicide when the arsphenamins are available, leads the author to deprecate intravenous use. The elimination of bismuth after injections of an oil suspension occurs at an unpredictable and variable rate, bearing some relation to eccentricities of absorption. The best eliminated products are the vegetable oil suspensions of iodin and quinine-containing bismuth salts. The author approves the use of massive doses of an insoluble bismuth salt at the outset of a course, not because of any immediate massive effect, as had been proposed, but because in this way the slow absorption is to some extent compensated for. Subsequent doses must be reduced. The author considers that where arsphenamin is used coincidentally there is no occasion for massive dosage or for intravenously administered bismuth. The most uniform absorption is secured with water-soluble bismuth compounds but these are by far the most painful and their limited depot-forming

value is also a drawback. Colloidal bismuth preparations are of value in the milder types of combined bismuth therapy. The daily dose of metallic bismuth by whatever salt introduced, should not in general exceed 25 to 30 mg. The average course should be about 1100 to 1300 mg. metallic bismuth in a vegetable oil suspension. The interval between courses with a water-soluble or colloidal preparation should not exceed six weeks, and with the intramuscular use of an oil-suspended salt in amounts of 1000 mg. metallic bismuth and over, the interval should not be less than eight to ten weeks.

The Treatment of Epidermophytosis.—CASTELLANI (*Lancet*, 1928, ii, 595) discusses a new treatment in certain types of ringworm infections, mainly those caused by *Epidermophyton inguinale* and *E. rubrum*. He recommends the employment of a fuchsin paint prepared by adding to the ordinary laboratory basic carbol fuchsin stain 1 per cent boric acid, 5 per cent acetone and 10 per cent resorcin. This may be applied in full strength as often as twice daily. The writer catalogues the variety of cases in which this treatment is unusually valuable, namely: (1) ringworm of the feet and toes particularly with secondary pyogenic infection; (2) cases of epidermophytosis simulating moist eczema; (3) epidermophytic pompholyx; (4) mycotic pruritus of the anus and vulva. In ordinary ringworm of the body and groin the use of Whitfield's ointment appears preferable.

Liver Diet in Acne Vulgaris and in Furunculosis.—SUTTON (*Arch. Dermat. and Syph.*, 1928, 18, 887) treated 27 cases of acne vulgaris and furunculosis with a diet high in liver. He employed both the fresh and the powdered extract. The quantity of extract ranged from 24 to 72 doses over an average period of twelve days. The best clinical response was obtained in the patients with pale moist flabby skins who presented deep-seated lesions of the indolent type.

Some Remarks on the Bactericidal Properties of Zinc Oxid. HAXTHAUSEN (*Brit. J. Dermat. and Syph.*, 1928, 40, 497) believes that in addition to the known properties of drying, protection, and binding of irritants, zinc oxid possesses bactericidal qualities that enhance its value in cutaneous conditions. The author noticed that while talcum and kaolin had no effect on the growth of staphylococci, strewing zinc oxid over the surface of a Petri-dish containing agar inoculated with staphylococci caused small but distinct sterile zones about each deposit of zinc oxid. No effect was noted in the case of *Bacillus pyocyaneus*, but slight effects on *Bacillus coli*. However, the resistant *Bacillus subtilis* showed a distinct sterile zone. Most noticeable were the zones for staphylococci and streptococci particularly when the pH of the medium was reduced from 7.5 to 5.5. Commercial zinc oxid was found to exhibit a stronger action than the chemically pure drug. The action on bacteria appears to be due to the development of acid by the strain of organism, the consequent partial dissolution of the chemical, and the formation of a compound that can give off free zinc ions. The author concludes that there is every reason to believe that a similar bactericidal process takes place *in vivo* when zinc oxid is applied as an ointment to the skin, and the action is especially pronounced where staphylococci and streptococci are involved.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Early Clinical Diagnosis of Cervical Cancer.—The early clinical diagnosis of carcinomatous material is often a very difficult matter. Of course a section of tissue can be examined under the microscope and a diagnosis readily made in most cases, but where the case is being considered from the standpoint of operability, this type of diagnosis is of little aid in determining just where the malignant epithelium ends and the normal cells begin. In the case of the cervix, even if a section were made from the border of the growth, this would only show the conditions at that particular point and would give no information relative to the extent throughout the remainder of the circumference of the cervix. In their clinic in Vienna, according to SCHILLER (*Zentralbl. f. Gynäk.*, 1928, 52, 1886), considerable work has been done with vital staining of the tissues as a means of differentiating malignant from benign cells. It was found to be of little value because all living cells took the stain deeply whether they were carcinomatous or normal, while only necrotic cells failed to take the stain. On the other hand, it was found that when Lugol's solution was applied to the cervical and vaginal epithelium the normal cells were stained a deep dark-brown color in a few seconds, whereas pathologic cells were not discolored. This differentiation is supposed to be due to the difference in glycogen content in normal and in carcinomatous cells. The test is considered specific only in that what becomes discolored is normal epithelium. Lack of staining does not necessarily mean that the tissue is carcinomatous, although it usually is, but it may be due to hyperkeratotic epithelium which is frequently seen associated with uterine prolapse. Such epithelium contains only a very small amount of glycogen and therefore does not become stained upon the application of an iodine solution.

Operation Versus Irradiation in Cervical Cancer.—These gynecologists who still prefer operation to irradiation in the treatment of cancer of the cervix are few and far between, especially in this country. In Europe, however, there seem to be several clinics in which the radical operation is still performed with a fair amount of frequency. In comparing the relative value of hysterectomy and irradiation, FORGUE (*Am. J. Surg.*, 1928, 5, 44), of France, states that when dealing with a beginning case which appears definitely operable from both the technical point of view (mobile uterus and flexible vaginal fornices) and the clinical point of view (no contraindication in the state of the patient)

he believes that panhysterectomy offers advantages which compensate for the operative risk. It is logical to employ preparatory radium treatment before the hysterectomy and it carries an additional factor of safety in that it sterilizes the cervicovaginal passages, but in these favorable cases he believes that one can and should remain in the domain of surgery alone. In practice, this supplementary preoperative radium therapy presents one of two difficulties, namely, the patient who has submitted to treatment by irradiation will have a tendency to be content with this treatment on account of the amelioration of symptoms, and if the patient be a private case she may refuse to pay the expense of both radium therapy and surgery. He states that his opinion is only provisional and may be modified by improved radium technique with correspondingly improved results.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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On Nonhypophyseal Affections of the Chiasma.—HENNING RONNE (*Acta Ophthalmologica*, 1928, 6, 332-343) refers to the crossing of the macular fibers in the posterior chiasma angle and points out that in hypophyseal affection developing in the meridian behind the chiasma there macular fibers will be first involved. The clinical consequence of this is development of a bitemporal hemianopic central scotoma. These small defects in the field of vision are not noticed by the patient and may be overlooked. "The site of the macular fibers in the posterior chiasma angle is, also in another respect, of diagnostic significance, namely, in differential diagnosis between tractus-hemianopia and hemispheric hemianopia. Hemianopia originating from the optic tract is frequently due to tumorous formation, and the tract being of relatively short extension, the pressure will, in the majority of cases, reach the proximal chiasma angle; at this juncture the macular fibers will be involved, the result being reduction of central vision in one or both eyes. Reduction of visual acuity is, therefore, the best diagnostic criterion in differentiating between tractus hemianopia and hemispheric hemianopia, for in the latter form of hemianopia visual acuity is always normal." The various affections which, according to the author's experience, develop in the chiasmal region are tumorous formation within the chiasm itself, primary neuritis within the chiasm, optic nerve atrophy seen in tabes dorsalis (of which the author has observed 4 cases) and multiple sclerosis. Frontal lobe tumor may also give direct compression symptoms in the chiasma in a manner similar to hypophyseal tumor resulting in an irregular hemianopic visual field.

Ocular Tuberculosis and Constitution.—GRONHOLM, V. (*Acta Ophthalmologica*, 1928, 6, 297-309) refers to intra-ocular tuberculosis alone,

including chronic tuberculous uveitis, scleritis, and keratitis and the affections which arise in sequel to these. The etiology of these conditions can but rarely be verified by bacteriologic or inoculation test. The evidence of ocular tuberculosis at the Helsingfors University Eye-Clinic amounted to about 0.3 per cent. The age distribution of 100 cases of ocular tuberculosis was as follows— 66 per cent became manifest in the ages between fifteen and thirty years and most frequently between twenty-one and twenty-five years, while the disease was of comparatively rare occurrence before puberty and after the thirtieth year of age. The mean age of incidence for ocular tuberculosis is in the twenty-third year in either sex. The proportion of males to females affected were 1 to 3. Pulmonary tuberculosis could be demonstrated in only 18 of the cases, being found twice as often in men as in women. Affection of the cervical or bronchial glands, or of both, was of frequent coincidence with ocular tuberculosis, being demonstrated in 55 of the 100 cases. His observations indicated that ocular tuberculosis attacks apparently healthy individuals with an abated or fairly benign tuberculosis of some other organ, most frequently in the lymphatic vascular system, rarely in the lungs.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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A Comparative Study of Chronic Sinusitis with End Results Following Intranasal Operations.—In presenting his observations on a group of cases limited to: (1) Chronic suppurative sinusitis; (2) chronic hyperplastic ethmoiditis; (3) polypoid degeneration of the mucosa, and excluding those instances of chronic empyema involving only the maxillary sinus, REAVES (*Arch. Otolaryngol.*, 1929, 9, 23) emphasizes the difficulties of diagnosis and dwells upon the relative merits of the various methods of examination, including history, nasopharyngoscopy, transillumination, radiography and visual acuity tests. After a consideration of the symptomatology, the author, in treating of the etiology, discusses infection as the cause of chronic suppurative sinusitis; the rôle of exogenous irritants, low-grade infection, endogenous toxins and metabolic disturbances in the chronic hyperplastic forms of ethmoiditis; and the allergic and infectious phases of polypoid degeneration. Following a detailed description of his intranasal operative technique, his results from surgical intervention are tabulated. It was found that of the total number of operations performed, including 57 for chronic suppuration, 54 for chronic hyperplasia and 39 for polypoid degeneration, 1.3 per cent of cases were not improved, 10.6 per cent were unsatisfactory and 85.2 per cent were satisfactory. In concluding, Reaves calls attention to a definite pathologic condition of the nasal mucosa with a tendency to formation of polypi and rarefaction of bone and a fairly constant group of symptoms. This condition differs from true

hyperplasia by the absence of thickened bone and headache. He further states that the degree of headache associated with chronic suppuration depends on the condition of the bone; and that most cases of chronic sinusitis will clear up after ventilation and drainage have been established.

The Incidence of Nasal Sinusitis with Diseases of the Ear.—"Though the problems of deafness in the adult are better understood, prevention and treatment are less effective than in children. If progressive deafness is to be mastered, the periods of its inception and pre-inception will furnish the most promising grounds for research. Any deafness may become progressive in some degree, and it is not yet known when or why any deafness may presage permanent or progressive deafness. For these reasons, a study of the ears of children is desirable, and any correlation that may be established between the disease of the ear and factors heretofore thought incidental should be of some value." As it is recognized that an intimate relation between the ears and the nose and nasopharynx exists, FOWLER (*Arch. Otolaryngol.*, 1929, 9, 159) by charts, tables and discussion, presents the results of an exhaustive investigation relative to the incidence of paranasal sinusitis and aural disease occurring in 100 consecutive cases in children. From his analysis of those observations, the author summarizes that complete histories, tests and stereoroentgenograms give invaluable data for the study and treatment of otologic lesions; that 57 per cent of the cases showed moderate or severe involvement of the nasal sinus spaces; that 71 per cent exhibited pathologic changes in the ethmoid septa; that 86 per cent revealed pathologic processes in the sinuses; that the chronicity of the suppuration in the ear was directly proportional to the involvement of the sinus spaces, and indirectly proportional to that in the ethmoidal septa; that diseases of the nasal sinuses, and of the sinuses of the ear, were intimately associated, and prevention, alleviation and cure of one necessitates the prevention, alleviation and cure of the other; that in virtually all of the children there had been inflammation not only of the ears, but also of the nasal sinuses; and that the coëxistence of otitis and active or latent sinus infection is not coincidental.

Inflammatory Affections of the Orbit of Nasal Origin.—DAVIS (*J. Laryngol. and Otol.*, 1929, 44, 164) found that the commonest cause of orbital inflammation of nasal origin was suppuration of the frontal sinus in adults (16 cases) and ethmoidal suppuration in children (7 cases). In no instance was the orbital involvement due to extension of the infection from the maxillary or sphenoidal sinuses. Frontal sinus suppuration when it involves the orbit produces a characteristic downward and outward displacement of the eyeball, whereas ethmoidal suppuration displaces the eyeball outward and forward. Diagnosis is made on intranasal examination, radiography and differentiation from cysts, mucocele and neoplasm. The treatment depends on the source of infection and the presence or absence of an orbital abscess. If an abscess is present, immediate incision and drainage of both the abscess and the affected sinus is indicated. If the orbital inflammation is non-suppurative, drainage of the affected sinus usually suffices. Occasional complications are cavernous sinus thrombosis and secondary optic atrophy.

RADIOLOGY

UNDER THE CHARGE OF

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Diathermy in Pneumonia.—Reports from all parts of the country and from abroad show a steady increase in the use of diathermy in pneumonia, according to STEWART (*Arch. Phys. Ther., Roentg. Ray, Radium*, 1928, 9, 437). After six years experience Stewart makes a definite claim for a lessened mortality in treated cases. In the average case he advises treatment every four hours, except during the early morning, with electrodes sufficiently large to cover the involved area, anteriorly and posteriorly, at 1400 to 1800 ma. At first caution was advised in cases complicated with empyema, but now Stewart not only continues but intensifies the treatment, once the patient has passed the critical stage of his pneumonia.

Ultraviolet Irradiation in Skin Diseases.—NORRIS (*Arch. Phys. Ther., Roentgen Ray, Radium*, 1928, 9, 448) remarks sarcastically that ultraviolet rays have achieved a remarkable vogue and are being applied indiscriminately for an imposing list of conditions ranging from flat feet to shinning scalps. Norris has tried it without favorable consequences in ichthyosis, common warts, vitiligo, epidermolysis bullosa and certain other conditions. However, in psoriasis, eczema, particularly acute and weeping types, if there is not much infiltration, and in acne vulgaris, varicose ulcers with associated dermatitis, nevi, and lichen planus, Norris finds it very useful. It is of value in certain cases of generalized pruritus, and in several instances of chronic urticaria Norris has given the major credit to ultraviolet irradiation, universally applied, for perfect recoveries. In ivy poisoning and generalized arsenical dermatitis it has reduced pruritus, dried the areas, and promoted recovery. It has produced gratifying results in impetigo contagiosa, likewise in erythema multiforme. Norris goes on to state emphatically that in certain skin conditions ultraviolet rays are distinctly harmful, as, for example, in such diseases as xeroderma pigmentosum. Technique of applying the irradiation is a matter of importance and requires training and experience.

Roentgenologic Study of the Abdominal Viscera.—MOODY and VAN NUNES (*Am. J. Roent. and Rad. Ther.*, 1928, 20) have carried out a study of abdominal viscera, especially the liver and spleen, by simple roentgenography. They find that long livers having their lower tip in the pelvic cavity as much as 5 cm. below the interiliac line are normal. More men than women have long livers. The lower border of the spleen

is most commonly found opposite the upper half of the third lumbar vertebræ, but long spleens with their lower border opposite the fourth lumbar vertebra are not uncommon, especially in men, and without any history of malaria. There is some evidence that exercise decreases the spleen in man, and that loss of blood given for transfusion has the same effect.

Extra-abdominal Affections Giving Gastrointestinal Symptoms, with Special Reference to the Ménière Syndrome.—With evident approval, CRANE (*Radiology*, 1928, 11, 447) quotes W. J. Mayo as follows: "The stomach is the alarm box of the abdomen, and the hose is often turned on the alarm box instead of the real conflagration." This, says Crane, is one reason why cases of abdominal angina, the visceral crises of the erythemas, mucous colitis and Ménière's disease continue to be operated on for supposed appendicitis, ulcer or gall stones. No one of these is common but in the aggregate they assume considerable clinical importance. For many years Crane has been impressed with the frequency with which cases of Ménière's disease come in for examination of the gastrointestinal tract. Even physicians themselves when suffering from this condition rarely exercise the personal detachment necessary to disregard the call of the digestive tract.

To suggest an adequate reason for negative roentgenologic findings may be a defense reaction on the part of the roentgenologist. If he has not found the trouble it is because he does not know how—that is the attitude of some patients and occasionally of some surgeons. Negative Roentgen ray findings may be the outcome of some of the finest work in roentgenology, and yet a patient may sum up the whole, painstaking investigation with contemptuous brevity in: "Oh, they found nothing." Study negative findings: it is in this field that future Roentgen ray discovery may be expected. Behind every negative finding at apparent variance with the symptoms lies a worth-while diagnostic problem. If the roentgenologist will but exercise his training in the general diagnosis of internal disease, he will acquire increased precision and will less often be lured by the mirage so perfectly illustrated in Ménière's syndrome.

Cholecystography and Transduodenal Drainage.—In an extensive series of cases SNOW (*Am. J. Roent. and Rad. Ther.*, 1928, 20, 358) found that more than 90 per cent that had both duodenal drainage and the Graham test, gave similar results in indicating a normal or abnormal condition. A gall bladder which responds normally both to the Graham test and duodenal drainage is usually normal at operation. Failure to obtain B bile by the drainage test usually means failure to visualize the gall bladder with dye and the viscus is usually found at operation to be diseased. Gall bladders containing stones usually yield pathologic bile by the drainage test and often no B bile. A gall bladder which is faintly visible before and after dye and does not empty after fatty food, is definitely abnormal; in this series a hydrops was found in such cases and the drainage test yielded no B bile.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Focal Necrosis of Liver.—Various explanations have been offered to account for the irregular localization of focal necroses of the liver in the infectious diseases. The action of toxic substances and the presence of vascular thrombi have usually been indicated as the cause of these liver lesions. EDINGTON (*J. Path. and Bacteriol.*, 1929, 32, 1) encountered an endemic among guinea pigs due to *Bacillus ærtrycke*. In studying the organs from the fatal cases he observed the frequent presence of focal necrosis in the liver. He was unable to determine the presence of vascular thrombi, and the cellular infiltration by large monocytes was secondary to the process of necrosis. He was unable to find a direct relation between the lesions and localized aggregations of bacteria. Subsequently, he undertook an experimental study to determine whether bile stagnation was in any way related to the focal dissemination of the necrosis. Guinea pigs were operated upon, the common bile duct ligated, and then given a subcutaneous inoculation with *Bacillus ærtrycke*. These animals showed focal necroses within eighteen hours after the inoculation. Animals which alone were given *ærtrycke* and killed within twenty-four hours showed no focal necroses. Likewise animals in which the bile duct was ligated but not inoculated showed no necroses. The author was able to produce similar lesions by the use of *Bacillus enteritidis*, streptococci, and *Bacillus diphtheriæ* or its toxin, in place of the *Bacillus ærtrycke*. The author believes that the toxins from these organisms produce a cloudy swelling of the liver cells which interferes with the proper escape of bile. This retention of bile assists in further damaging cells that have been rendered unstable by the bacterial poisoning.

Diffuse and Nodular Fibrosis of Adventitia of Aorta (Rheumatic Periaortitis).—BARNARD (*J. Path. and Bacteriol.*, 1929, 32, 95) studied a single case of rheumatic aortitis arising in a young man, aged twenty-three years, who gave a history of recurrent attacks of rheumatic fever. The fatal illness was related to cardiac failure associated with a chronic endocarditis of the mitral and aortic valves. The aorta showed fibrous thickening in its thoracic portion. The fibrosis varied from nodular thickenings both in the intima and adventitia to the diffuse connective-tissue hyperplasia extending over the larger part of the vessel. This fibrosis also extended along some branches of the abdominal aorta. The microscopic analysis failed to reveal recent cellular infiltration, but showed an increase in the connective tissues on the outer side of the aorta

and to some extent entering the middle coat. The author points out that a differential diagnosis between syphilis, periaortitis nodosa, and rheumatic lesions must be made. The absence of any other lesions of a syphilitic nature, and the lack of aortic changes as found in syphilis rules out this condition. Likewise there was no evidence of periarotitis nodosa on any arteries of the peripheral system. He finds that the lesions which he described were similar to those described by Klotz in 1912, where it was shown that localized and diffuse fibroses upon the aortic wall are the outcome of rheumatic inflammatory processes in which their early stage was accompanied by a nonsuppurative cellular response.

Chronic Peptic Ulcer of the Esophagus.—The esophagus may occasionally suffer ulceration similar to the lesions which are found in the stomach and duodenum. The esophageal ulceration, however, is very rare, STEWART and HARTFALL (*J. Path. and Bacteriol.*, 1929, 32, 9) stating that only a single case had been encountered in over 10,000 autopsies performed during the last eighteen years. However, others give a higher incidence, some amounting to 1 in 200 cases. The peptic ulcer arises in the lower portion of the esophagus, usually at the border of the cardiac orifice. The ulcer is prone to be chronic, showing a fibrosis in the floor and accompanied by little or no inflammatory exudate. The process of necrosis may extend through the walls of the esophagus, leading to perforation. In a few instances the development of carcinoma at the edge of the ulcer has been described. The authors report the case which they observed at autopsy arising in a man, aged fifty-three years, who gave a history of digestive disturbance with an occasional vomiting of blood. At autopsy the ulcer was found to be of large size, showing a perforation just above the level of the cardia. This perforation passed through a dense mass of fibrosis and entered the right pleural cavity. It was interesting that the authors found the presence of two large patches of gastric mucosa in the upper esophagus just below the level of the cricoid cartilage. Although misplacements of the gastric mucosa are not uncommon in the esophagus, the question arises whether these anomalies are associated with the development of the chronic ulcer.

Pathogenesis of Intestinal Amebiasis in Kittens.—REES (*Arch. Path.*, 1929, 7, 1) has undertaken to study the early stages of the intestinal lesions arising in experimental amebic dysentery. He introduced a new method for infecting the animals with *E. histolytica* grown upon cultures. In place of the usual procedure of infecting the animals by means of a rectal tube, the author, by means of a laparotomy ligated the lower portion of the rectum and injected the cultures directly into the bowel. The author found that lesions appeared forty hours after the operation, and became quite severe after ninety hours. Widespread destruction of mucosa took place, and it appeared as if the effect of the injected amebæ was directly upon the surface membranes and not by the development of small ulcers in the crypts of the glands. The first lesions were in the vicinity of the ileocecal valve, and when ulceration occurred the submucosa did not appear to be invaded beyond that of the mucosa. The injury results from the presence of a cytolytic toxin.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Problem of Automobile Exhaust Gas in Streets and Repair Shops of Large Cities.—BLOOMFIELD and ISBELL (*Pub. Health Repts.*, 1928, 43, 750) conducted an extensive field and laboratory study, which is best given in their own summary: This survey was undertaken to ascertain whether or not a health hazard from carbon monoxid existed in the streets of our large cities, inside of autobusses and in repair shops. Fourteen of the largest cities in the country were visited, having a combined population of over 19,000,000 and 250 samples of air were obtained for carbon-monoxid analysis. These samples were analyzed by the iodine-pentoxid method, using a liquid-air cooling tube, which was shown to be necessary in order to eliminate gasoline vapor, a substance which tends to vitiate the results of the analysis. Our street samples were taken in such a manner as to approach the most congested conditions that may exist at a busy traffic intersection. Hence, it is felt that these results indicate the maximum hazard from automobile exhaust gas that may exist today in our metropolitan thoroughfares. The average of 141 tests made in city streets at peak hours of traffic showed a contamination of 0.8 part of carbon monoxid per 10,000 parts of air. Only 24 per cent of all the street samples had more than 1 part of carbon monoxid in 10,000 of air, and in only one location, a covered passageway, was there as much as 2 parts per 10,000. Samples taken inside of autobusses yielded even lower concentrations of carbon-monoxid gas. The figures for street air, when viewed in the light of present-day standards of exposure to carbon monoxid, do not reveal the existence of a health hazard from this source in our city streets. The only individual who may possibly be exposed to a health hazard from inhaling street air containing automobile exhaust gas is the traffic officer. This potential hazard may be minimized by diminishing the duration of exposure at the most congested traffic stations. Of the 102 tests made in 27 garages in the 14 cities visited the average carbon-monoxid content was found to be 2.1 parts in 10,000. More than half of the samples (59 per cent) contained over 1 part of carbon monoxid, and 18 per cent of all the samples contained over 4 parts of this gas in 10,000 parts of air. These results for repair shops show a dangerous condition that demands the serious consideration of those concerned. This hazard in repair shops may be reduced to a minimum by not allowing the motors of automom-

biles to run longer than thirty seconds unless the car is in necessary motion or the exhaust is connected to the outside air by a direct airtight outlet of ample caliber. Without such outlet no automobile engine should be allowed to run indoors, except to reach its berth or to leave by the shortest route. All of these samples were taken in garages of considerable size. The great danger to life is unquestionably in the small private garage containing one or two cars. Under any circumstances the discharge of an automobile exhaust into a roofed inclosure should be regarded as a hazardous act.

A Further Study of Experimental Black Tongue with Special Reference to the Black Tongue Preventive in Yeast.—GOLDBERGER, WHEELER, LILLIE and ROGERS (*Pub. Health Repts.*, 1928, 43, 657) on the treatment of black tongue in dogs is covered by the following summary and conclusions: The black-tongue-producing potency of a basic experimental diet and of three modifications was tested 33 times in 31 dogs with the production of 33 separate attacks of black tongue. Only 1 of these attacks developed at the end of a period longer than sixty-one days. Experimental black tongue is due to a dietary deficiency which is capable of being corrected by something contained in yeast. This something, or black-tongue preventive, in yeast is inactivated or destroyed by heat sufficient to char the yeast; retains its preventive potency in large measure, if not entirely, after heating in the steam autoclave at a pressure of 15 pounds for seven and a half hours; is adsorbed from an acidulated aqueous extract of either dried yeast or of yeast first autoclaved at a pressure of 15 pounds for two and a half hours by English fuller's earth. It cannot be identified with any of the older well-recognized dietary essentials, but is believed to be identical with the thermostable substance of Smith and Hendrick. The black-tongue preventive and the pellagra preventive are both present in yeast. Taken in conjunction with certain other evidence pointing to the fundamental identity of black tongue and pellagra, this association strengthens the probability that the black-tongue preventive and the pellagra preventive, or vitamin P-P, are identical.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 15, 1929.

The Permeability of the Mammalian Erythrocyte to Glycerol and its Bearing on Certain Theories of Cell Permeability.—M. H. JACOBS (from the Department of Physiology, University of Pennsylvania). The differential permeability of the cell, that is, its tendency to exclude some substances and to admit others with different degrees of readiness, has in the past frequently been explained by one of two theories: the pore theory and the solubility theory. According to the first, the chief

determining factor in cell permeability is the "effective size" of the penetrating molecules; according to the second their solubility in lipoids.

The mammalian erythrocyte shows a behavior with glycerol which appears to be most plausibly explained by the pore theory. Using with suitable precautions the hemolysis method of determining the rate of penetration of this substance, it can be shown that the rate is very different for different species and is affected in a characteristic way by temperature changes, the general, though not the invariable, rule being that in those erythrocytes which are most readily permeable at body temperature the rate of penetration is not greatly retarded by lowering the temperature, while in those which are much less permeable the temperature effect is very great.

As examples of the first condition are the erythrocytes of the mouse and man where the ratio of the penetration rate at one temperature to that at a temperature 10° lower (Q_{10}) is in the vicinity of 1.4, which is only slightly higher than that characteristic of a simple diffusion process. At the other extreme are the erythrocytes of the cat, dog, pig and especially of the sheep and ox with Q_{10} values in the vicinity of 3 or greater. The erythrocytes of the rat, rabbit and guinea pig fall in an intermediate class.

It is believed that these differences in the magnitude of Q_{10} are not due to fundamentally different mechanisms of penetration in the different cases but rather to different degrees of modification of ordinary diffusion processes. A relatively simple hypothesis to account for the observed facts is that as the temperature is lowered the pore size is decreased (possibly as the result of increased adsorption). In cases involving small molecules or larger pores, or both, diffusion is little interfered with by lowered temperature but in cases where the pores are small or the molecules are large, or both, the temperature effect is comparatively great.

In support of this view it may be mentioned that for the ox, which of all of the species studied shows the highest Q_{10} value for glycerol, the Q_{10} value for water is that of a simple diffusion process and for the relatively small urea molecule is only a little higher, that is, 1.4. On the other hand, the human erythrocyte which shows for glycerol a Q_{10} value approximately equal to that for urea and not much greater than that for water shows according to Masing a very high one with glucose.

It must be emphasized that the conclusions here stated do not apply to substances which are freely soluble in lipoids and do not necessarily apply to cells other than the erythrocyte which is a highly specialized and in some respects a very peculiar type of cell.

Micrurgic Studies on Tissue Culture Cells.—GEORGE ST. DE RENYI and M. J. HOGUE (from the Department of Anatomy, University of Pennsylvania). The following results were obtained by the authors in studying skeletal muscle fibers from chick embryos of eight to ten days' incubation, cultivated in fluid culture media:

The outgrowing muscle buds represent muscle fibers of a very low grade of differentiation. They do not contain myofibrils, at least it is impossible to show them by optical methods. The buds can be shown to contain only threadlike mitochondria, nuclei, and granules of uncertain nature, in addition to the hyalin sarcoplasma. The surface of the

fibers, even on the delicate growing ends, is covered with sarcolemma. This is firmer than the surface film of other cells. The muscle buds do not become stretched by growth, as Lewis believes. The rapid shortening of the fibers when stimulated mechanically is a real contraction. It has been shown that the sarcoplasm alone is responsible for this contraction, which is not typical, but twitchlike and is not followed by relaxation. No organic connections can be demonstrated between the muscle fibers and the fibroblasts of the culture.

The Effect of Iodin and Thyroid Feeding on the Histology of the Thyroid Gland of the Dog.—W. B. MOSSER (from the Department of Surgical Research University of Pennsylvania). Normal adult dogs were fed iodine and desiccated thyroid substance. Iodine ingestion produced an increase in the colloid content of the gland with compression of the cells. Prolonged iodine administration produced a stage of exhaustion in the gland characterized by a loss of architecture and disintegration of the cells. Regeneration of the gland occurs after a rest period. Ingestion of desiccated thyroid substance produced an hypertrophy and hyperplasia of the cells lining the acini.

The Mechanism of Ovulation in the Rabbit.—M. H. FRIEDMAN (from the Department of Physiology, University of Pennsylvania). The rabbit differs from other laboratory rodents in that it does not ovulate spontaneously, but only after coitus. Neither artificial insemination nor injections of sperm or semen are successful in provoking ovulation. Yet, ovulation regularly follows coitus with a vasectomized buck and can be produced by rubbing the vulva of a female in heat. Marshall holds the view that the phenomenon is nervous reflex in nature. There has been no decisive work to confirm or to refute this hypothesis. It was with such purpose that these experiments were undertaken.

To test the possibility of intrinsic reflexes from the vagina through the uteri and tubes to the ovaries, it was decided to remove the greater part of the genital tract in the female and note the effect on ovulation. In four rabbits, therefore, both Fallopian tubes and both uteri were removed entirely; leaving behind only that portion of the vagina caudad to the neck of the bladder. Four weeks after operation, these four females were mated. At autopsy three days later, fresh corpora lutea in addition to several corpora hemorrhagica were found in the ovaries of each of these animals. Subsequent histologic examination confirmed these gross findings and showed without question that the removal of the whole genital tract, with the exception of that portion of the vagina between the neck of the bladder and the external orifice, does not prevent ovulation in the rabbit.

As a result of the findings in these experiments, the possibility of an humoral mechanism was more seriously considered. Consequently, a series of ovarian transplants were made, both ovaries being removed at the time of operation, so that the operated animals possessed no ovarian tissues except that transplanted to the rectus muscle. From five to seventeen weeks after the operation, 13 of the 15 animals so prepared accepted coitus as shown by the finding of sperm in the vaginal smear. In each instance, the animal was killed and autopsied about twenty hours after coitus. In 9 of the 13 animals accepting coitus, one or more corpora hemorrhagica were found at the site of the

transplant. Histologic examination of these blood follicles, showed them to be typical corpora hemorrhagica with retained ova. In addition to the corpora hemorrhagica large, unruptured follicles were seen in 7 of the 9 animals and 2 instances genuine fresh corpora lutea were found. In one case, in which 3 corpora hemorrhagica and 2 corpora lutea occurred, the follicles had apparently ruptured into the peritoneal cavity so that no search for the discharged egg was made. In the other instance, however, the follicle had discharged into the surrounding tissues. In several sections ventral to the equator of this discharged follicle, the recently expelled egg was seen. These findings demonstrate clearly that ovulation in the rabbit can occur without the participation of the ovarian nerves, and indicate the presence of some humoral mechanism.

From the recent work of Engle and Smith, and of Zondek and Ascheim, who were able to induce superovulation in the rat by the daily transplantation of the anterior lobe of the hypophysis, came the suggestion that this gland may be involved in the process of ovulation in the rabbit. Following the technique of Engle and Smith, I have transplanted as many as 15 rat pituitaries into a rabbit without provoking ovulation. Due to the almost prohibitive cost of using more glands than this, it was deemed expedient to use a different source of the hormone. On the basis of the recent reports of Zondek and Ascheim which indicate the presence of some substance in the urine of pregnant women, which simulates in action the hormone of the anterior lobe, a series of injection of such urine specimens were made. After the injection of 12-cc. doses of urine from a pregnant woman into a rabbit for four days, large numbers of corpora lutea were found in the ovaries at autopsy. This result was secured using 7 different specimens of urine on 7 rabbits. In one case, the urine was obtained from a woman three months pregnant. Five specimens of urine from nonpregnant women injected similarly gave negative results in 5 rabbits. At present, it is impossible to evaluate these results. They are however, sufficient justification for the undertaking of a statistical investigation to determine whether or not such urine injections may be used for the early diagnosis of pregnancy.

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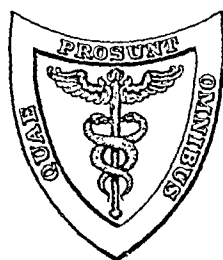
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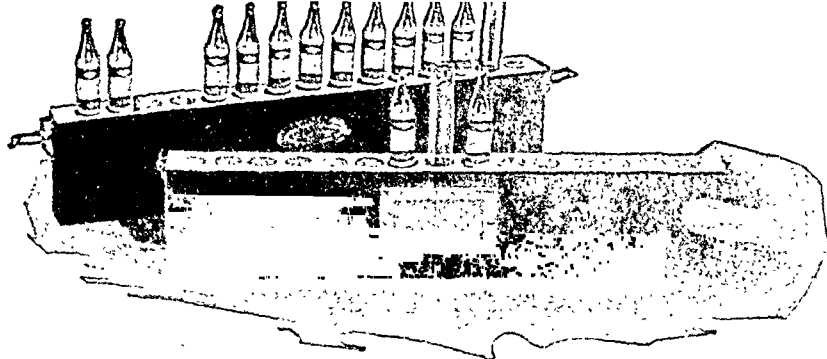
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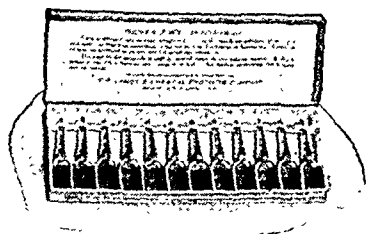
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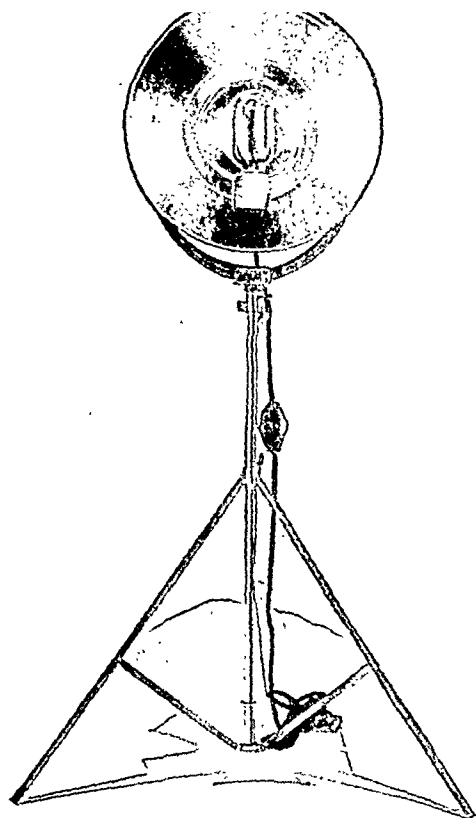
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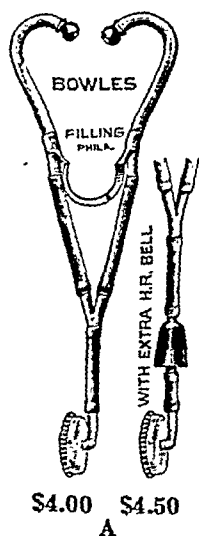
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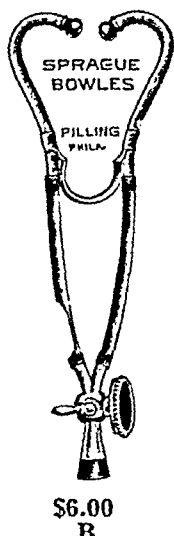
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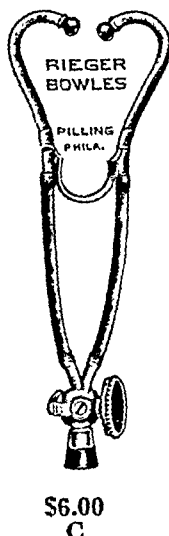
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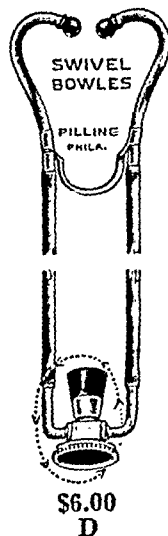
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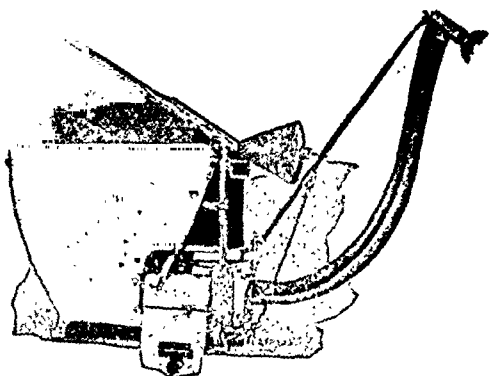
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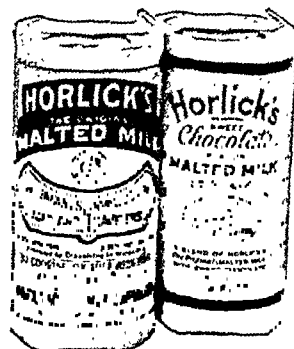


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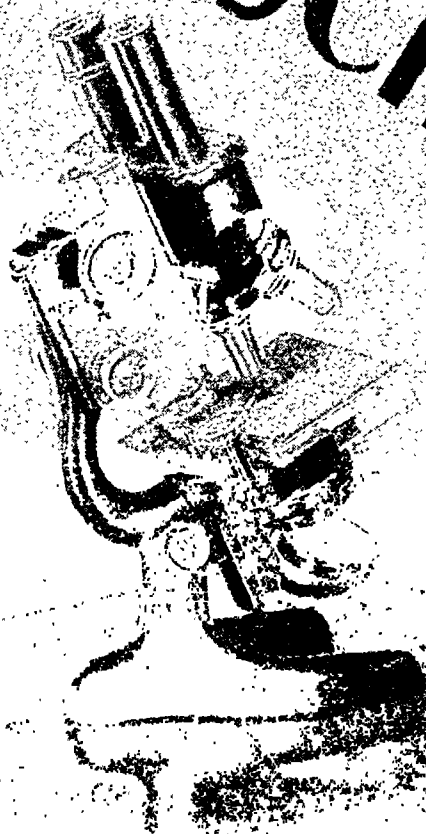
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Orthopedic Surgeon, Carney Hospital, Boston, Massachusetts.

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FROM THE PREFACE

*A*N arthroplasty is a highly technical operative procedure, which aims not only to restore motion to a joint, but also to preserve stability. The creation of an artificial joint by arthroplasty for the purpose of restoring motion to an ankylosed joint is one of the most notable advances of contemporary surgery. Until recent years, surgeons have believed that ankylosis in good position constituted the best curative result to be sought in certain traumatic or infectious joint lesions. With the development of surgical technique and particularly with the advancement of the specialties, operators, alert to the great disability caused by an ankylosed limb, have endeavored to restore motion to the joint by the use of many different operative procedures. The surgical methods devised and practised have shown a logical advance in keeping with the broader understanding of the pathology of ankylosed joints, until finally the method termed arthroplasty was evolved.

The clinical and scientific data that has gradually accumulated in the field of arthroplasty has now reached such extensive proportions that it is possible to ascertain the actual status of the procedure. Our object in presenting this treatise is to emphasize the fact that arthroplasty has become a standardized form of treatment for the mobilization of ankylosed joints. Such a conclusion has been reached from our wide personal experience in this field as well as from a careful study of the results reported by the prominent advocates of the method.

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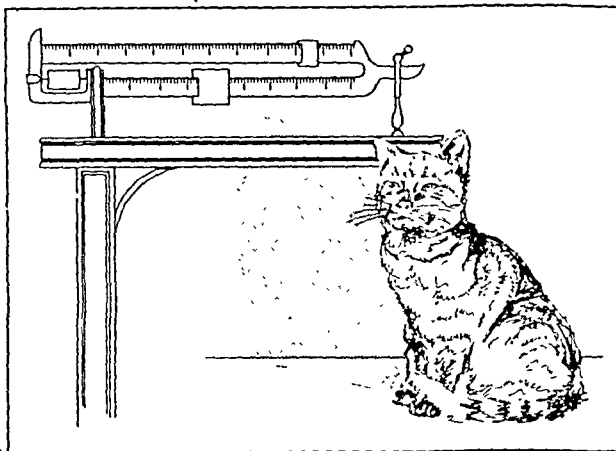
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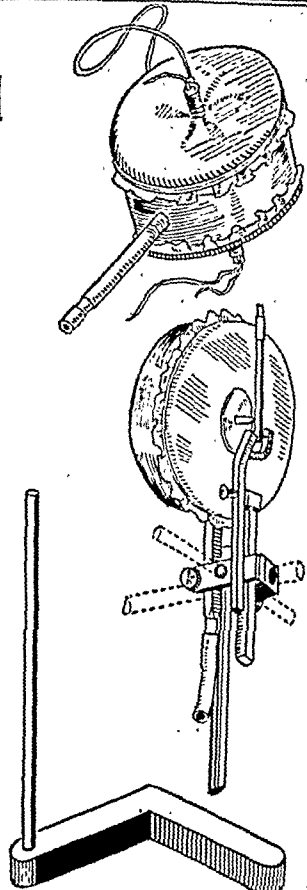
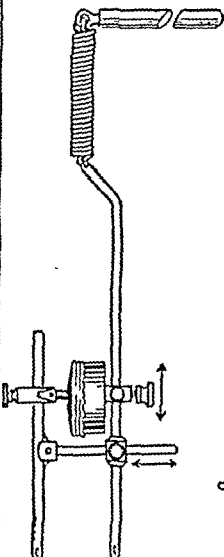
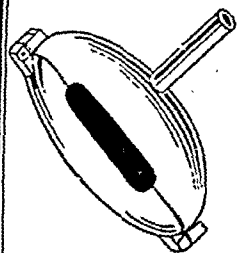
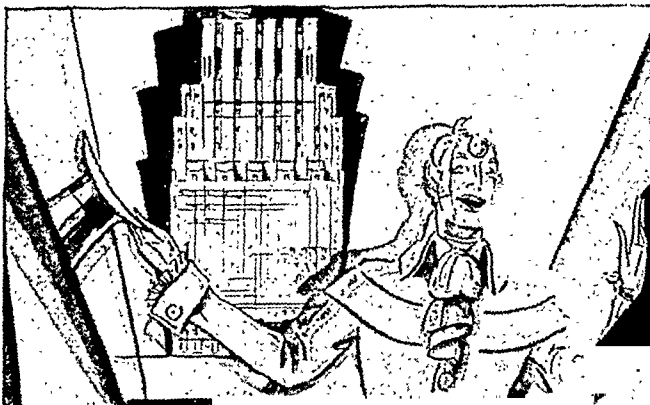
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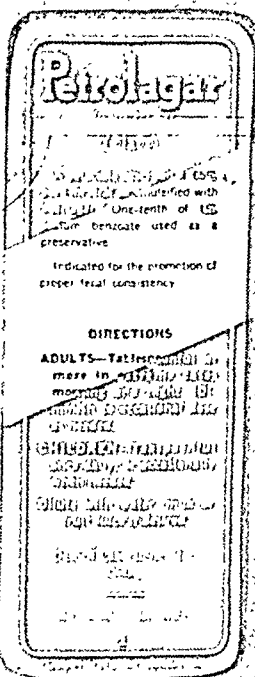
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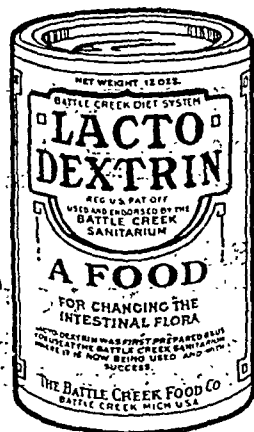
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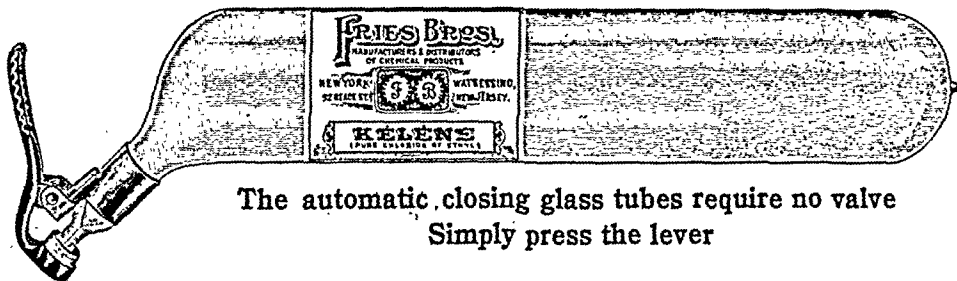
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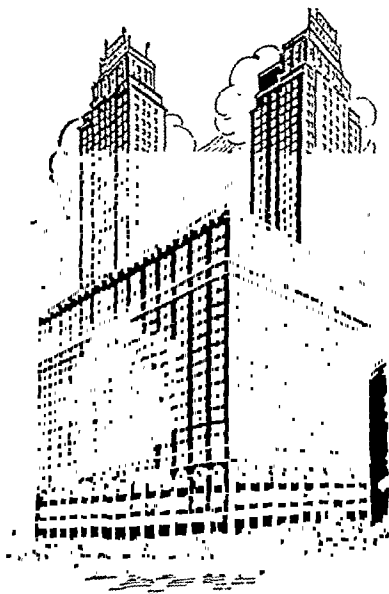
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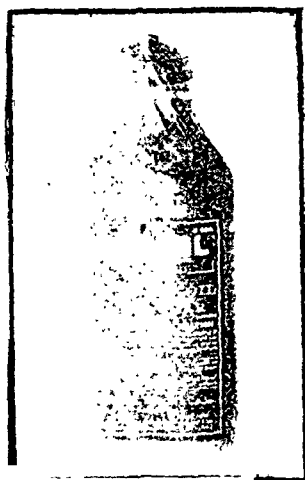
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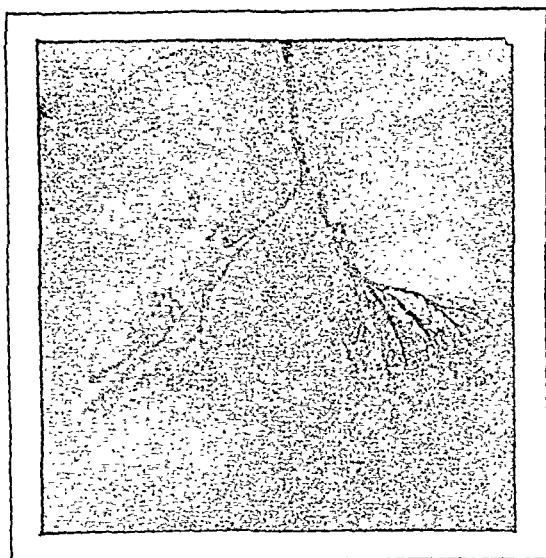
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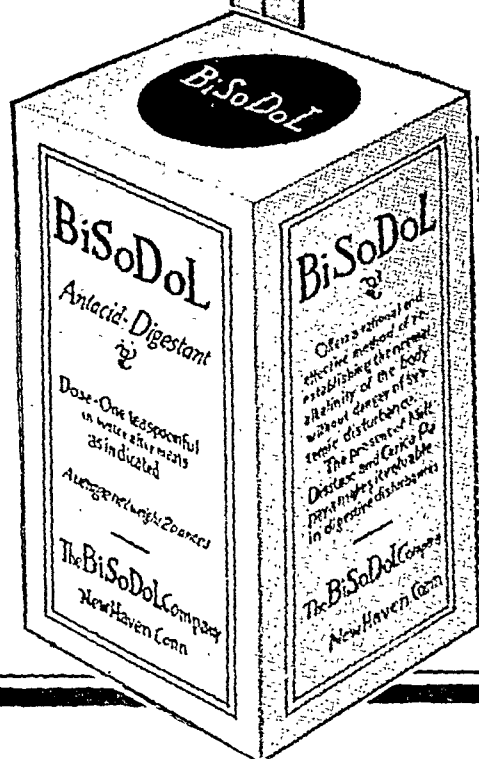
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are indicated in both

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THE HARRIS LABORATORIES, INC.
Tuckahoe, New York

